

PRODUCT MONOGRAPH

*Pr***Vagifem**[®]

17 β -Estradiol

Vaginal tablet with applicator, 25 μ g

Estrogen

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PrVAGIFEM®

Estradiol vaginal tablet, 25 µg estradiol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
vaginal	Vaginal tablet with applicator / 25 µg estradiol	lactose, maize starch, methylhydroxypropylcellulose, magnesium stearate and polyethylene glycol 6000

INDICATIONS AND CLINICAL USE

Vagifem® (estradiol vaginal tablet) is indicated for:

- The treatment of the symptoms of atrophic vaginitis due to estrogen deficiency. Addition of a progestin is not recommended.

Geriatrics (>65 years of age): Clinical studies of Vagifem® did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects.

Pediatrics (<18 years of age): Vagifem® is not indicated for use in the pediatric population.

CONTRAINDICATIONS

Vagifem® (estradiol vaginal tablet) is contraindicated in women with:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.
- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer
- Undiagnosed abnormal genital bleeding.

- Known or suspected pregnancy.
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Lactation

WARNINGS AND PRECAUTIONS

General

Risks and benefits of treatment with Vagifem[®] should be re-assessed at least annually. Vagifem[®] should only be continued as long as the benefits outweigh the risks.

Vagifem[®] is a topical, low-dose vaginal estrogen therapy product (see **Action and Clinical Pharmacology – Pharmacokinetics – Absorption**). The following warnings and precautions associated with oral estrogen therapy should be considered in the absence of comparable data with other dosage forms of estrogens.

Carcinogenesis and Mutagenesis

Breast cancer

There is a need for caution in prescribing estrogens of any kind to women with a strong family history (first degree relative) of breast cancer or women who have nodules, fibro cystic disease or abnormal mammograms and/ or atypical hyperplasia at breast biopsy.

In the oral *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.²

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see **Contraindications**).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients.

Instructions for regular self-examination of the breasts should be included in this counseling.

Endometrial hyperplasia & endometrial carcinoma

There is no systemic effect under local estrogen treatment with Vagifem[®], the addition of a progestin is not recommended.

Endometrial histology was evaluated in 5 clinical trials conducted in the USA and Canada. Endometrial biopsies were evaluated at the end of the study in nonhysterectomized subjects. Table 1 provides a summary of endometrial biopsies taken at the end of 3 short-term studies and Table 2 provides a summary of endometrial biopsies taken at the end of 2 long-term studies. Only one woman treated with Vagifem[®] developed simple endometrial hyperplasia. There were two cases of endometrial hyperplasia in women treated with conjugated estrogen vaginal cream (2g containing 625 µg/g of conjugated equine estrogen), and no cases of endometrial hyperplasia in women treated with placebo.

Table 1 - Endometrial Biopsies taken at the end of the Short-Term Studies n (%)			
	Vagifem[®]	Conjugated estrogen vaginal cream	Placebo
<i>Treated</i>	199	79	47
Biopsies	89	49	21
Insufficient Tissue	20 (22)	21 (43)	3 (14)
Results			
Normal			
Atrophic	64 (72)	15 (31)	18 (86)
Weakly Proliferative	0 (0)	4 (8)	0 (0)
Proliferative	3 (3)	7 (14)	0 (0)
Abnormal			
Endometrial hyperplasia			
-Simple	1 (1)	1 (2)	0 (0)
-Complex	0 (0)	1 (2)	0 (0)
Other			
Polyp	1 (1)	0 (0)	0 (0)

Table 2 - Endometrial Biopsies taken at the end of the Long-Term Studies n (%)	
Treated	Vagifem®
	158
Biopsies	79
Insufficient Tissue	23 (29)
Results	
Normal	
Atrophic	53 (68)
Weakly Proliferative	1 (1.3)
Proliferative	2 (2.6)
Abnormal	0 (0)

Ovarian Cancer

Recent epidemiologic studies have found the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of continuous combined oral conjugated estrogens (CEE) and medroxyprogesterone acetate (MPA) is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.^{1,4,5} The results of the WHI trial indicate that the use of oral *estrogen-alone* and oral *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.^{1,2}

Blood Pressure

Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Endocrine and Metabolism

Glucose and lipid metabolism

Although no effect of low dose vaginal estradiol supplementation has been seen on glucose tolerance, fluid retention, elevation of blood pressure or other liver or endocrine functions,

women with predisposition to or signs indicating an effect on those variables could indicate caution.

Hyperlipidemia has been reported in women on other types of estrogen replacement therapy, but it has not been observed in women using Vagifem[®].

Genitourinary

Vaginal Bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Women should be advised to inform their physician if irritation, pain, discharge, unusual or unexpected bleeding occur during treatment.

Women with signs of ulceration or severe inflammation due to unresponsive atrophic vaginitis, withdrawal from treatment should be considered and appropriate investigations should be conducted.

Applicator Trauma

Trauma induced by the Vagifem[®] applicator may occur, especially in patients with severely atrophic vaginal mucosa. After gynecological surgery, any vaginal applicator should be used with caution and only if clearly indicated.

Uterine leiomyomata

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

Vaginal Infection

Vaginal infection is generally more common in postmenopausal women due to the lack of the normal flora seen in fertile women, especially lactobacillus, and the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial therapy *before* initiation of **Vagifem[®]**. If a vaginal infection develops during the maintenance phase of the treatment, appropriate therapy should be instituted. The next dose of **Vagifem[®]** should be inserted once the therapy is completed.

Hematologic

Venous thromboembolism

Available epidemiological data indicate that use of oral estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

The benefits and risks of hormone replacement therapy should be carefully weighed when prescribing **Vagifem**[®] to women with a risk factor for thrombotic disorders. The physician should be alert to the earliest manifestations of thrombotic disorders. If these occur or are suspected, estrogen therapy should be discontinued immediately. Women with a positive family history and women with a history of thromboembolic disorders during pregnancy or in association with estrogen use should be kept under special observation.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m²) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic

Gallbladder diseases

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

Neurologic

Cerebrovascular insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

Dementia

Available epidemiological data indicate that the use of combined oral estrogen plus progestin in women age 65 and over may increase the risk of developing probable dementia.

Epilepsy

HRT may cause an exacerbation of epilepsy.

Renal

Fluid retention

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Special Populations

Pregnant Women: Estrogen should not be used in pregnancy. Any possibility of pregnancy must be ruled out before prescribing Vagifem[®]. If pregnancy occurs during Vagifem[®] treatment, the medication should be discontinued immediately.

Nursing Women: Estrogens should not be used during lactation. Vagifem[®] should not be prescribed for nursing mothers.

Pediatrics (<18 years of age): Vagifem[®] is not indicated for use in the pediatric population.

Geriatrics (>65 years of age): Clinical studies of Vagifem[®] did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects.

Conditions which need Supervision:

Due to the local administration of low dose estradiol in Vagifem[®], the recurrence or aggravation of some conditions is less likely than with systemic estrogen treatment, such as:

- Leiomyomata (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Hypertension
- Liver disorders (e.g. liver adenoma)

- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis.

Therapy should be discontinued if any of the following situations is discovered:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine- type headache
- Pregnancy

Monitoring and Laboratory Tests

Before Vagifem[®] is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

Women treated with **Vagifem[®]** should be advised to keep their regular medical checkups to assess the need for continuing therapy.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Reproductive system and breast disorders

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea ; vaginal itching/discharge; dyspareunia ; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Comparative Studies

In an open-labelled, multi-centre, comparative clinical trial conducted in Canada, women were treated with either Vagifem[®] (N=80) or conjugated estrogen vaginal cream (N=79) for up to 6 months. Vagifem (25 µg estradiol) was administered daily for 2 weeks, then twice weekly with at least 3 days between each application, for the remaining 22 weeks; 2 g of the comparator drug, containing approximately 1.25 mg conjugated estrogen, was given daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for up to 24 weeks. Table 3 lists the percentage and reasons for discontinuation from the study.

Table 3 - Reasons for discontinuation / Study duration - 24 wks (%)		
Reason	Vagifem[®] N = 80	Conjugated estrogen vaginal cream N = 79
Adverse Event	4 (5)	14 (18)
Non-compliance with protocol	2 (2.5)	8 (10)
Other	2 (2.5)	3 (4)
Total	8 (10%)	25 (32%)

Placebo Controlled Studies

A placebo-controlled comparison study was done in the U.S., in which 230 patient were randomized to receive either placebo, 17 β -estradiol 10 μ g vaginal tablets, or Vagifem[®] (25 μ g estradiol). Patients inserted one tablet intra-vaginally each day for 14 days, then one tablet twice weekly for the remaining 10 weeks. All patients were assessed for vaginal symptoms.

Overall, **Vagifem[®]** is well tolerated, is comparable to placebo in overall incidence of treatment-emergent adverse events, has not demonstrated a potential for causing adverse events associated with endogenous levels of estrogen that differs from other topical hormone therapies and has not demonstrated a potential for causing adverse events associated with cumulative dosing in long-term therapy extending to 64 weeks.

In 8 clinical trials, conducted in North America and Europe, involving 438 women treated with **Vagifem[®]** for atrophic vaginitis, including 115 women treated for 52 weeks, approximately 21% of women experienced a treatment emergent adverse event that could possibly or probably be related to **Vagifem[®]**.

Table 4 lists the treatment-emergent adverse events reported by 5% or greater of the women in short term (up to 24 weeks) studies conducted in Canada and the United States.

Table 4- Frequency of Treatment-Emergent Adverse Events (TEAE) Regardless of Drug Relationship						
Events	Vagifem[®]		Conjugated estrogen vaginal cream		Placebo	
	n	(%)	n	(%)	n	(%)
No. Treated	199		79		47	
No. with TEAE	122	(61)	55	(70)	26	(55)
Female Reproductive						
Pruritus Genital	7	(4)	5	(6)	0	(0)
Candidiasis	9	(5)	1	(1)	1	(2)
Postmenopausal Bleeding	4	(2)	13	(16)	2	(4)
Breast Pain Female	5	(3)	7	(9)	0	(0)
Perineal Pain	2	(1)	6	(8)	0	(0)
Vaginitis	7	(4)	3	(4)	3	(6)

Table 4- Frequency of Treatment-Emergent Adverse Events (TEAE) Regardless of Drug Relationship						
Respiratory						
URI	14	(7)	7	(9)	2	(4)
Influenza	3	(2)	4	(5)	0	(0)
Body as a Whole						
Headache	17	(9)	4	(5)	3	(6)
Abdominal Pain	9	(5)	4	(5)	2	(4)
Back Pain	8	(4)	0	(0)	3	(6)
Gastrointestinal						
Flatulence	3	(2)	4	(5)	1	(2)

Other Clinical Trial Adverse Drug Reactions (<5%)

The following adverse events were reported at an incidence of <5% for Vagifem[®] regardless of drug relationship.

Skin/Appendages: Acne; Dermatitis contact; Nail disorder; Pruritus; Pruritus genital; Rash; Skin disorder; Skin ulceration; Urticaria

Musculoskeletal: Arthralgia; Arthritis; Arthritis aggravated; Arthrosis; Bone Disorder; Myalgia

Central Nervous System: Dizziness; Hypertonia; Hypoaesthesia; Migraine; Involuntary muscle contractions; Paraesthesia

Vision Disorders: Blepharitis; Conjunctivitis

Psychiatric Disorders: Agitation; Anxiety; Increased appetite; Depression; Insomnia; Libido decrease; Nervousness; Somnolence

Gastrointestinal: Abdominal pain; Constipation; Diarrhea; Diverticulitis; Dyspepsia; Flatulence; Gastroesophageal reflux; Nausea; Tooth disorder; Vomiting

Endocrine Disorders: Goiter

Cardiovascular: Heart murmur; Hypertension; Palpitation

Vascular Disorders (non-CVD): Cerebrovascular disorder; Thrombophlebitis leg superficial

Respiratory System: Bronchitis; Bronchospasm; Coughing; Pharyngitis; Rhinitis; Sinusitis

Urinary System: Dysuria, Haematuria; Micturition frequency; Urethral disorder; Urinary incontinence; Urinary tract infection

Reproductive Disorders: Abdominal pain; Breast disorder (not otherwise specified); Breast pain; Endometrial hyperplasia; Leukorrhea; Perineal pain; Postmenopausal bleeding; Vaginitis; Vaginitis ulcerative; Vulva discomfort

Foetal Disorders: Spinal malformation

Neoplasm: Basal cell carcinoma; Breast fibroadenomas; Renal carcinoma; Uterine fibroid; Vaginal neoplasm benign

Hearing and Vestibular: Ear disorder NOS; Earache

Liver and Biliary: Gama-GT increased, Hepatitis, SGOT and SGPT increased

Metabolic and Nutritional: LHD increased; Oedema legs; Phosphatase alkaline increased

Platelet, bleeding & clotting: Haematoma; Purpura

Immune system: Herpes simplex; Infection.; Fungal infection; Candidiasis genital; Lymphadenopathy

Body as a whole: Allergic reaction; Allergy; Aesthenia; Back pain; Carpal tunnel syndrome; Fatigue; Fever; Headache; Hot flushes; Influenza-like symptoms; Leg pain; Neck rigidity; Oedema peripheral; Pain

Post-Market Adverse Drug Reactions

The following events have been spontaneously reported during Vagifem[®] use in clinical practice. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Neoplasm benign and malignant:
Breast cancer; endometrial cancer

Immune system disorders:
Hypersensitivity

Metabolism and nutrition disorders:
Fluid retention

Psychiatric disorders:
Insomnia; depression

Nervous system disorders:

Migraine aggravated

Vascular disorders:

Deep venous thrombosis

Gastrointestinal disorders:

Diarrhea

Skin and subcutaneous disorders:

Urticaria; rash erythematous; rash pruritic

Reproductive system and breast disorders:

Endometrial hyperplasia; vaginal irritation; vaginal pain; vaginismus; vaginal ulceration

General disorders and administration site conditions:

Drug ineffective

Investigations:

Weight increase; blood estrogen increase

DRUG INTERACTIONS

Overview

Vagifem[®] is a topical vaginal estrogen therapy product. The following drug-interactions are based on the experience of systematic estrogen treatment.

Enzyme inducers, (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, or rifampicin) can enhance estrogen metabolism, resulting in breakthrough bleeding or vaginal spotting.

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Drug-Drug Interactions

No Drug-Drug Interactions with Vagifem[®] have been reported.

See **Warnings and Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

Drug-Food Interactions

No Drug-Food Interactions with Vagifem[®] have been reported.

Drug-Herb Interactions

No Drug-Herb Interactions with Vagifem[®] have been reported.

Physicians and other health care providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products.

Drug-Laboratory Interactions

There are no studies investigating Drug-Laboratory interactions with Vagifem[®].

The pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used.

Vagifem[®] may be used in women with or without an intact uterus.

During treatment, especially during the first 2 weeks, minimal absorption may be seen however, as plasma estradiol levels after the first 2 weeks usually do not exceed postmenopausal levels; the addition of a progestin is not recommended.

Recommended Dose and Dosage Adjustment

Treatment may be started on any convenient day.

Initial dose: 1 vaginal tablet daily for 2 weeks

Maintenance dose: 1 vaginal tablet twice a week with a 3 or 4 day interval between doses

Missed Dose

If a patient misses a dose, it should be administered as soon as possible. If it is close to the patient's next scheduled dose, the missed dose should be skipped, and the patient should continue with her normal schedule. The patient should not take two doses at the same time.

Administration

Accidental injury during administration of Vagifem[®] may occur if the applicator is introduced too high into the vagina. **Women should be shown how to administer Vagifem[®] correctly.** No incidences of applicator injury were reported in the clinical trials of Vagifem[®].

Vagifem[®] (estradiol vaginal tablet) is gently inserted into the vagina as far as it can comfortably go without force, using the supplied applicator. Detailed instructions for use are provided in *Part III: Consumer Information*.

OVERDOSAGE

No cases of overdose have been reported

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. In general, excessive doses of estrogen may result in nausea, vomiting, abdominal cramps, headache, dizziness and general malaise.

The dose of estradiol in Vagifem[®] is very low compared with oral estrogen products. Treatment of overdose should be symptomatic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

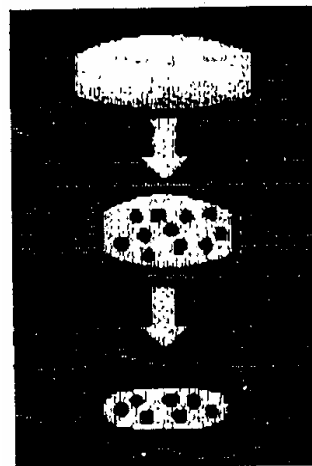
Vagifem[®] (estradiol vaginal tablet) is a hydrophilic, cellulose-derived matrix tablet which hydrates upon contact with moisture, releasing 17 β -estradiol (Figure 1). The estradiol in Vagifem[®] is chemically and biologically identical to the endogenous human estradiol and is therefore classified as a human estrogen. 17 β -estradiol is the primary estrogen and the most active of the ovarian hormones.

Figure 1. Diffusion of estradiol from a dry vaginal tablet

Dry Tablet

Upon contact with vaginal mucosa, a gel layer forms on the surface.

As moisture permeates the tablet, it is eroded and soluble estradiol diffuses out of the gel layer.



Pharmacodynamics

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 the tissue of the reproductive tract, breast, pituitary, hypothalamus, liver and bone of women. Estrogens regulate growth, differentiation and function 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.

Endogenous 17 β -estradiol induces and maintains the primary and secondary female sexual characteristics. Most of the activities of 17 β -estradiol appear to be exerted via binding to specific estrogen receptors in target cells of tissue. The steroid-receptor complex is bound to the cell's DNA and induces synthesis of specific proteins.

The hormone deficient state associated with menopause leads to atrophic changes in the urogenital epithelial and subepithelial tissues. Vaginal blood flow is reduced, causing decreased lubrication during sexual arousal rendering the tissue more susceptible to trauma. Thinning of the vaginal mucosa occurs, cellular and glycogen production declines, decreasing the colonization of lactobacilli and thus lactic acid production. The usual acidity of the vagina, which serves as a potent defence mechanism, is lost. Symptoms associated with the atrophic changes are vaginal dryness, genital itching and burning and dyspareunia. The goal of local estrogen therapy is to provide sufficient estrogen to reverse atrophic changes in the local tissues and relieve associated symptoms.

Maturation of the vaginal epithelium is dependent on estrogen. Estrogen increases the number of superficial and intermediate cells as compared to basal cells.

Estrogen keeps pH in the vagina down to around 4.5 which enhances normal bacterial flora, *Lactobacillus Doderlein* predominating.

Pharmacokinetics

Absorption:

Estrogens are well absorbed through skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal route of estrogen delivery avoids first-pass metabolism. After administration of Vagifem[®], 17 β -estradiol is absorbed from the vaginal mucosa.

A single-centre, randomized, double-blind, comparison study was conducted in U.S. to investigate the effects of Vagifem[®] treatment on serum hormone concentrations. Subjects were treated with Vagifem[®] daily for 2 weeks followed by twice weekly administration for 10 weeks. Serum estradiol (E₂) and estrone (E₁) levels were measured after the first dose at 1, 2, 4, 5, 6, 7, 8, 10, 12 and 24 hours after administration at each study visit. E₁S (estrone sulfate) and FSH levels were determined after the first dose at 6, 12 and 24 hours after administration at each study visit. Study visits were scheduled on the first day of dosing after 1, 2, 4, 8, and 12 weeks of

treatment. A total of 28 healthy women with atrophic vaginitis received Vagifem[®] of which 22 completed the study.

Figure 2 illustrates the serum E₂ levels following the first dose after 2 and 12 weeks of treatment. This study showed that the vaginal application of Vagifem[®] over a 12-week period did not result in accumulation of estradiol as measured by the AUC₀₋₂₄ (Table 6). C_{max} of serum estradiol was constant from the first day of treatment (week 0) to the end of treatment (week 12). There was a small statistically significant increase in mean E₁S (estrone sulfate) concentrations during the 12 weeks of therapy. The mean concentrations over the 24-hour period after dosing at weeks 0, 2 and 12 ranged from 360-469 pg/mL, 572-673 pg/mL, and 470-556 pg/mL, respectively, for women treated with Vagifem[®]. Mean FSH (averaged over the 24-hour sampling period) decreased significantly, with a median change of -9.0 IU/L at week 2 and -4.4 IU/L at week 12.

Figure 2: Serum E₂ Levels (Mean ± 2x Standard Error) After Application of Vagifem[®] at Weeks 0, 2, and 12

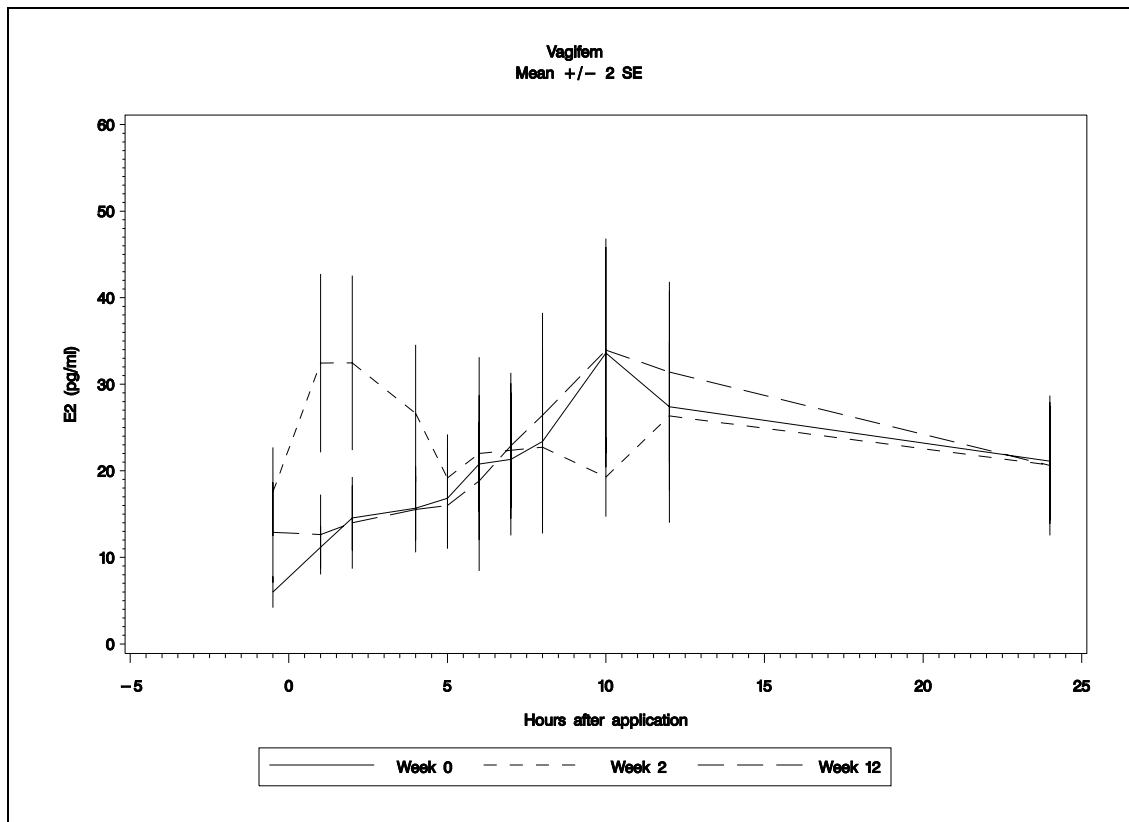


Table 5 - Mean ± Standard Deviation for AUC, C_{max}, T_{max} for E2 and E1 at Weeks 0, 2 and 12 following Vagifem[®] treatment			
Parameter	Week	Vagifem[®]	
		Estradiol	Estrone
AUC (pgh/mL)			
	0	538 ± 265	649 ± 230
	2	567 ± 246	744 ± 267
	12	563 ± 341	681 ± 271
C_{max} (pg/mL)			
	0	51 ± 34	35 ± 12
	2	47 ± 21	39 ± 13
	12	49 ± 27	35 ± 12
t_{max} (h)			
	0	15 ± 9	14 ± 9
	2	8 ± 8	7 ± 8
	12	13 ± 6	12 ± 11

Distribution:

Circulating, unbound estrogens are known to modulate pharmacological response. Estrogens circulate in the blood bound to sex-hormone binding globulin (SHBG) and albumin.

Metabolism:

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

Excretion:

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

STORAGE AND STABILITY

Store in a dry place, protected from light. Store between 15°C - 30°C. Do not refrigerate. Store in original package.

Keep in a safe place out of the reach of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Vagifem[®] (estradiol vaginal tablet) is a small, white, film-coated tablet containing 25.8µg of estradiol hemihydrate equivalent to 25µg of estradiol.

Each tablet contains the following inactive ingredients: lactose monohydrate, maize starch, methylhydroxypropylcellulose, magnesium stearate and polyethylene glycol 6000.

Each white tablet is 6mm in diameter and is contained in a single-use high density polyethylene/polypropylene applicator. Each tablet-filled applicator is packaged separately in a laminated blister package.

Vagifem[®] is available in cartons of 15 pre-loaded applicators.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

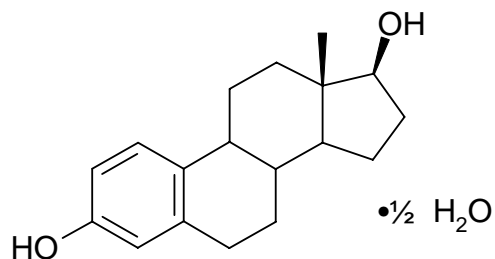
Proper name: estradiol hemihydrate

Chemical name: oestra-1,3,5(10)-triene 3, 17 β -diol hemihydrate

Molecular formula: $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$

Molecular mass: 281.4

Figure 3: Structural formula



Description: White or almost white crystalline powder or colourless crystals

Solubility: Practically insoluble in water

Melting point: 173 - 179°C

CLINICAL TRIALS

Efficacy and Safety Studies

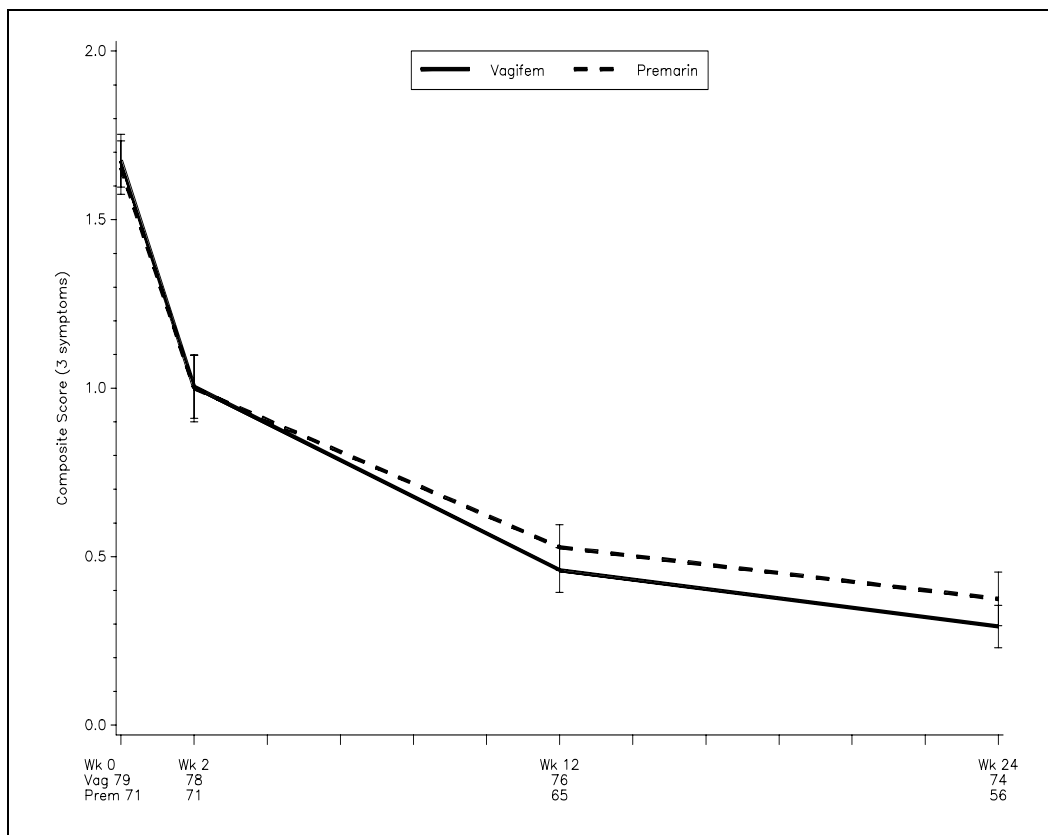
Comparative Studies

In an open-labelled, multi-centre, comparative clinical trial conducted in Canada, women were treated with either Vagifem[®] (N=80) or conjugated estrogen vaginal cream (N=79) for up to 24 weeks. Vagifem (25 µg estradiol) was administered daily for 2 weeks, then twice weekly with at least 3 days between each application, for the remaining 22 weeks; 2 g of the comparator drug, containing approximately 1.25 mg conjugated estrogen, was given daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for up to 24 weeks. Relief of atrophic vaginitis was evaluated by grading dryness, soreness and irritation on a 4-point scale as 0=none, 1=mild, 2=moderate and 3=severe. A composite score, calculated as the average score of the three symptoms, was used to compare the efficacy of the two products. Of the patients entering into the treatment phase of the study, 10% in the Vagifem[®] group discontinued their treatment and 32% discontinued in the comparator group.

Vagifem[®] was no different from the conjugated estrogen vaginal cream in relieving symptoms of postmenopausal estrogen deficient-related atrophic vaginitis (Table 6). The average severity score of the three symptoms over time for the comparator study is shown in Figure 4. Women assessed the ease of use of the products and overall, Vagifem[®] was rated easier to use and more acceptable than conjugated estrogen vaginal cream.

Table 6 - Relief of Vaginitis - Mean score of vaginal dryness, soreness and irritation Observed Data Analysis				
Week		Vagifem[®]	Conjugated estrogen vaginal cream	P-value (95% CI)
0	N	79	71	0.733 (-0.17, 0.20)
	Mean	1.68	1.66	
12	N	76	65	0.496 (-0.30, 0.19)
	Mean	0.46	0.53	
	CHG	-1.22	-1.16	
24	N	74	56	0.482 (-0.32, 0.21)
	Mean	0.29	0.38	
	CHG	-1.38	-1.33	

Figure 4: The composite score over time for both treatments.

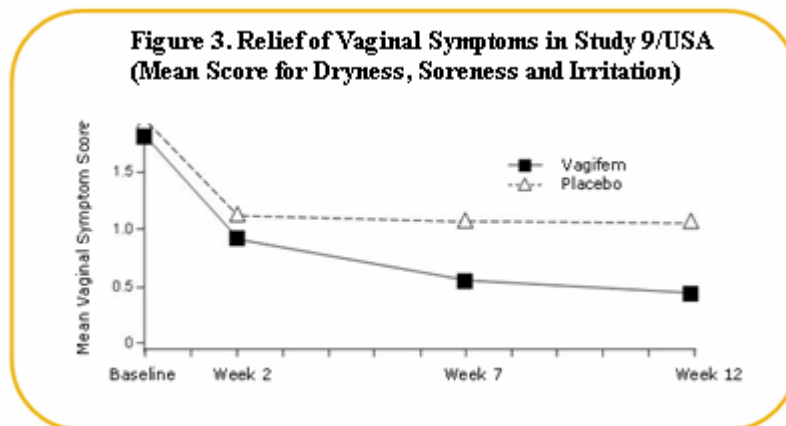


In four (4) North American clinical trials involving 53 women treated for 12 weeks, 43 for 24 weeks, 19 for 28 weeks and 101 treated for 52 weeks, all with **Vagifem**[®], and 79 women treated with conjugated estrogen vaginal cream for 24 weeks, the use of **Vagifem**[®] significantly increased the percentage of superficial and intermediate cells which was reflected in an increase in Maturation Value Index starting at week 2 of therapy. Consistent FSH decrease was seen with conjugated estrogen vaginal cream but not with **Vagifem**[®]. No clinically relevant systemic absorption was observed with **Vagifem**[®].

Placebo-Controlled Studies

A double-blind, multi-centered, placebo-controlled comparison study was conducted in the U.S. in which 230 patients were randomized to receive either placebo, 17 β -estradiol 10 μ g or **Vagifem**[®] (25 μ g estradiol). 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 using composite score. **Vagifem**[®] was more effective than placebo in the relief of symptoms of dryness, soreness and irritation associated with atrophic vaginitis (See Figure 5).

Figure 5: The composite score over time for Vagifem[®] versus Placebo



DETAILED PHARMACOLOGY

See *Action and Clinical Pharmacology* section under *Part I*.

Pharmacokinetics

See *Pharmacokinetics* section under *Part I*.

TOXICOLOGY

Exposure levels to estradiol and estrone following **Vagifem[®]** treatment are not outside the range seen in untreated postmenopausal women. The dosage of 25µg estradiol in **Vagifem[®]** (estradiol vaginal tablet) is low compared to natural production in fertile women and exposure is low compared to other methods of administering estrogen.

During long term maintenance therapy of up to 52 weeks no significant increase in the plasma concentrations of either E₂ or E₁ or E₁S over baseline was demonstrated.

Carcinogenicity / Teratology

Estradiol, given subcutaneously in mice, resulted in increased incidences of mammary, pituitary, uterine, cervical, vaginal, lymphoid and testicular tumours. Oral estradiol resulted in an increased incidence of mammary tumours. An increased incidence of mammary and/or pituitary tumours was noted in rats. Malignant kidney tumours occurred in intact and castrated males and in ovariectomized females but not in intact females. Diffuse fibromyomatous uterine and abdominal lesions were observed in guinea-pigs.

Estradiol is carcinogenic and teratogenic to the genital tract when given in high doses to animals. These effects are of minor significance to the postmenopausal use of the low exposure level of estradiol found in **Vagifem**[®].

Local Tolerance

A local vaginal tolerance study was conducted in rabbits. Minor bleeding was observed from the vagina after manipulation with the applicator. Post mortem hyperaemia and minor edema in the vagina was also observed. Microscopy showed that the tablet with or without estradiol did not cause irritation of the vaginal mucosa or the underlying tissue. The reaction observed in animals manipulated with the applicator only was induced mechanically. No reaction was ascribed to the tablets.

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PART III: CONSUMER INFORMATION

Pr **Vagifem**[®]
Estradiol vaginal tablets
25 µg

This leaflet is part III of a three-part "Product Monograph" published when Vagifem[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Vagifem[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Vagifem[®] (estradiol vaginal tablets) is used for the treatment of the symptoms of atrophic vaginitis due to estrogen deficiency.

Addition of a progestin is not recommended.

Vagifem[®] should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:

Vagifem[®] provides estrogen in and around the vagina. This helps to reduce dryness and discomfort you are experiencing in the urinary and genital area. Estrogen is made in your body by your ovaries. At some point, usually between the ages of 45 and 55, the ovaries decrease the amount of estrogen produced or stop producing estrogen all together. At this time, women go through the "change of life" or menopause. Monthly periods stop. Some women experience irritating feelings of warmth, heat and sweating (hot flashes).

Others find that the tissues of the vagina and urinary tract become thin and dry. This can be very uncomfortable and you may feel itching, burning and pain. Some women feel pain during sex. The same feelings may occur if the ovaries are surgically removed.

When it should not be used:

Vagifem[®] should NOT be used under these conditions:

- Known or suspected estrogen-dependent carcinoma
- Overgrowth of the lining of the uterus (endometrial hyperplasia)
- Known or suspected, or past history of breast cancer
- Unexpected or unusual vaginal bleeding
- Known or suspected pregnancy
- Breast feeding
- Have or have had blood clot disorders, including blood clots in the leg, lung or thrombophlebitis
- Allergic to estradiol or any of the ingredients in Vagifem[®]

What the medicinal ingredient is:

17β-Estradiol

What the important nonmedicinal ingredients are:

Lactose, maize starch, methylhydroxypropylcellulose, magnesium stearate and polyethylene glycol 6000

What dosage forms it comes in:

Vagifem[®] is available as vaginal tablets, supplied in cartons of 15 vaginal tablets. Each tablet is pre-loaded into the applicator and contains 25 µg estradiol.

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

Breast Cancer

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

Estrogens should not be taken by women who have a personal history of breast cancer.

In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

Vagifem has not been shown to increase risk of overgrowth of the lining of the uterus and cancer of the uterus.

Ovarian Cancer:

Use of estrogen alone and estrogen plus progestin therapies for 5 or more years has been associated with increased risk of ovarian cancer.

Heart Disease and Stroke

The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined oral estrogen plus progestin compared to women taking placebo.

In postmenopausal women taking oral estrogen-alone HRT, the results of the WHI indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking oral estrogen-alone compared to women taking placebo.

Abnormal Blood Clotting

Use of oral estrogen with or without progestin by menopausal woman is associated with increased risk of blood clots.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease

The use of oral estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

Dementia

Use of combined oral estrogen plus progestin in women age 65 and over is associated with increased risk of probable dementia.

BEFORE you use Vagifem[®] talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have been diagnosed with diabetes
- are pregnant or may be pregnant
- If you think you may have a vaginal infection

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

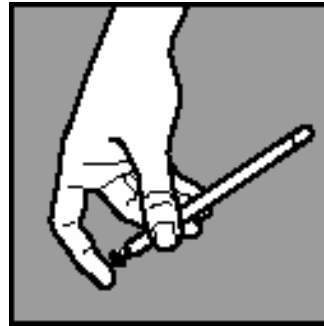
PROPER USE OF THIS MEDICATION

Usual dose:

In order to prevent injury, you need to be shown how to use Vagifem[®] correctly. Ask your doctor or pharmacist to demonstrate the proper use of Vagifem[®] applicator.

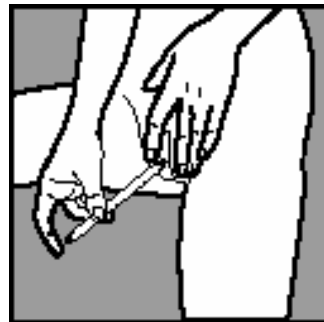
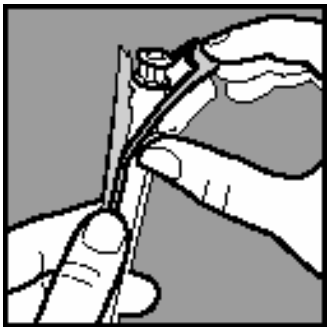
You can start using **Vagifem[®]** on any day of the week at any time of day you like. Once started, it is recommended that **Vagifem[®]** be used at that same time each day. Use 1 vaginal tablet each day for the first 2 weeks (7 vaginal tablets per week. A total of 14 vaginal tablets). Then, use 1 vaginal tablet twice a week with 3 or 4 days between doses (2 vaginal tablets per week).

The vaginal tablet is pre-loaded into the applicator. You can see this through the plastic bubble in the package.



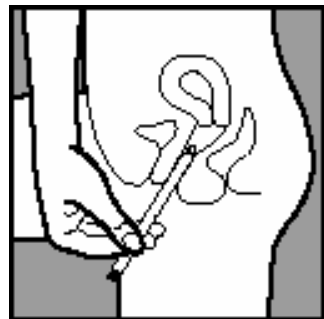
1. Wash your hands.

4. Hold the applicator with your thumb and middle finger. Leave your index finger free to press the applicator plunger.



2. Push the **Vagifem**[®] applicator through the foil backing (not through the plastic bubble) that says **Vagifem**[®] and Novo Nordisk.

5. With your free hand, hold open the skin at the vaginal opening.



3. Choose the position that is most comfortable for you. You may want to:

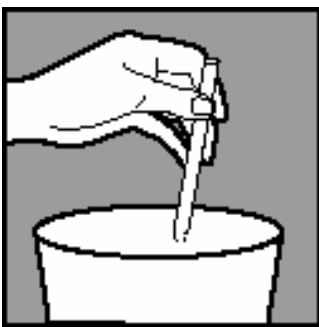
- sit on the edge of a chair with your knees apart,
- stand up with one foot raised on the edge of the tub or bed,
- squat
- lie down.

6. Gently slide the vaginal tablet end of the applicator into the vagina as far as it will comfortably go. This will be no more than 8 cm. Aim towards your lower back. **DO NOT FORCE.** You do not need to insert the entire applicator into your body. The plunger end of the applicator will be outside your body. The words **Vagifem**[®] and Novo Nordisk on the applicator will be outside your body.

Inserting **Vagifem**[®] is like inserting a tampon.



7. Use your index finger to gently push the plunger. This will release the vaginal tablet from the applicator onto the vaginal tissues. You will hear a clicking sound when the tablet is released.



8. Withdraw the applicator and discard in a waste basket. Do not flush the applicator down the toilet.

If **Vagifem**[®] is expelled immediately after use, it is recommended to insert another vaginal tablet.

Overdose:

No cases of overdose have been reported. In general, excessive doses of estrogen may result in nausea, vomiting, abdominal cramps, headache, dizziness, and general ill feeling (malaise). Call your doctor if you suspect an overdose.

Missed Dose:

If a dose is forgotten, it should be taken as soon as the patient remembers. A double dose should be avoided.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects were reported during clinical trials conducted on **Vagifem**[®].

- Genital infection with a fungus or vaginal inflammation
- Headache
- Nausea
- Abdominal pain (stomach), distension or discomfort

- Indigestion
- Vomiting
- Flatulence
- Vaginal bleeding, discharge or discomfort
- Breast edema, breast enlargement, breast pain or pain tenderness
- Peripheral edema (swelling of arms or legs)
- Upper respiratory tract infection (URI) and influenza
- Back pain

The following side effects were reported voluntarily by patients who used **Vagifem**[®]; hence, it is not possible to estimate their frequency or to establish a relationship with **Vagifem**[®]:

- Breast cancer
- Cancer of the lining of the uterus (endometrial cancer)
- Hypersensitivity (allergic reactions)
- Fluid retention
- Insomnia
- Depression
- Deterioration of present migraine
- Blood clots (deep venous thrombosis)
- Diarrhea
- Hives
- Rash
- Itching in and around the vagina (genital pruritus)
- Excessive growth of the lining of the womb (endometrial hyperplasia)
- Vaginal irritation, vaginal pain, painful spasm of the vagina or vaginal ulceration
- Drug ineffective
- Weight increase
- Increase in blood estrogen

Although Vagifem[®] is only used in the vagina to treat local urogenital symptoms of menopause, the risks associated with oral estrogen therapy in general should be taken into account.

Do not use Vagifem[®] after the expiration date printed on the package.

Speak to your doctor or pharmacist if you have further questions after reading this information.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
How often they happen	Symptom/possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor
		Only if severe	In all cases	
Common	Abdominal pain, nausea or vomiting		✓	
Uncommon	Breast lump		✓	
Uncommon	Crushing chest pain or chest heaviness			✓
Uncommon	Pain or swelling in the leg			✓
Uncommon	Persistent sad mood			✓
Uncommon	Sharp pain in the chest, coughing blood or sudden shortness of breath			✓
Uncommon	Sudden partial or complete loss of vision			✓
Uncommon	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			✓
Common	Unexpected vaginal bleeding		✓	
Uncommon	Yellowing of the skin or eyes (jaundice)			✓
Uncommon	Hypersensitivity			✓

These are not all the possible side effects of Vagifem[®]. For more information, ask your health care provider or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 1-866-234-2345
By toll -free fax: 1-866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Novo Nordisk Canada, at 1-800-465-4334

This leaflet was prepared by Novo Nordisk Canada Inc.

Last revised: September 26, 2007.

HOW TO STORE IT

Keep out of the reach of children. Keep Vagifem[®] at room temperature, between 15 and 30°C (59 - 86°F), away from heat and humidity. Do not refrigerate. Store away from direct sunlight. Do not store any of your medications near the cooking area of the kitchen, the shower area of the bathroom, or the glove compartment of your car as the temperature in these areas may go above normal room temperature from time to time.