PRODUCT MONOGRAPH

PrVagifem® 10

Estradiol 10 µg

Vaginal tablets with applicators

Estrogen

Novo Nordisk Canada Inc.
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PrVagifem® 10

Estradiol vaginal tablet, 10 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 / 10 µg estradiol	lactose monohydrate, maize starch, hypromellose, magnesium stearate and polyethylene glycol 6000

INDICATIONS AND CLINICAL USE

Vagifem® 10 (estradiol vaginal tablet) is indicated for:

- The treatment of the symptoms of vaginal atrophy due to estrogen deficiency.

Pediatrics (<18 years of age): Vagifem® 10 is not indicated for use in the pediatric population.

CONTRAINDICATIONS

Vagifem® 10 (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 or past thrombophlebitis
- Liver dysfunction or disease as long as liver function tests have failed to return to normal

- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Partial or complete loss of vision due to ophthalmic vascular disease
- Breastfeeding
- Porphyria

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at the **lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

Vagifem® 10 is a locally administered vaginal treatment containing 10 µg of estradiol and therefore the occurence of the conditions mentioned in the box above, is less likely than with estrogen products used for systemic treatment. However, since Vagifem® 10 is a hormone therapy product these risks should be considered.

General

Risks and benefits of treatment with Vagifem® 10 should be re-assessed at least annually. Vagifem® 10 should only be continued as long as the benefits outweigh the risks.

Vagifem® 10 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.

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 HT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

Generally, estrogen-progestin combined treatment is known to increase the density of mammographic images which may adversely affect the radiological detection of breast cancer.

The overall benefits and possible risks of hormone 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:
Women with intact uterus with abnormal bleeding of unknown etiology or women with an intact uterus who have previously been treated with unopposed estrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment with Vagifem® 10.

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Because Vagifem® 10 has not been associated with an increased risk of endometrial hyperplasia or uterine cancer **progestins are not usually needed for women with intact uteri using Vagifem® 10 alone**.

Ovarian Cancer:
Recent epidemiologic studies have found the use of hormone 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.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.

Blood Pressure:
Women using hormone therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HT 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® 10.

Thyroid
Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone (as measured by protein-bound iodine (PBI)), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).The minimal systemic absorption of estradiol with local vaginal administration (see Section 5.2 Pharmacokinetic Properties) is likely to result in less pronounced effects on plasma binding proteins than with systemic hormones.

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 vaginal atrophy, withdrawal from treatment should be considered and appropriate investigations should be conducted.

Applicator Trauma
Trauma induced by the Vagifem® 10 applicator may occur, especially in patients with severe vaginal athropy. 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® 10. If a vaginal infection develops during the maintenance phase of the treatment, appropriate therapy should be instituted. The next dose of Vagifem® 10 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 therapy should be carefully weighed when prescribing Vagifem® 10 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/m^2) 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 HT, 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
HT 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.

Hypercalcemia
Administration of estrogens may lead to severe hypercalcemia in patients with some types of cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Special Populations

Pregnant Women: Estrogen should not be used in pregnancy. Any possibility of pregnancy must be ruled out before prescribing Vagifem® 10. If pregnancy occurs during Vagifem® 10 treatment, the medication should be discontinued immediately.

Nursing Women: Estrogens should not be used when breastfeeding. Vagifem® 10 should not be prescribed for nursing mothers.

Pediatrics (<18 years of age): Vagifem® 10 is not indicated for use in the pediatric population.

Conditions which need Supervision:
The pharmacokinetic profile of Vagifem® 10 shows a very low absorption of estradiol during treatment (see *Pharmacokinetics* section). Due to this, the recurrence or aggravation of the conditions mentioned below is less likely than with systemic estrogen treatment:

- 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
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer

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

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

Vagifem® 10 is a locally acting low dose estradiol preparation and therefore the occurrence of conditions mentioned above is less likely than with systemic estrogen treatment.

Monitoring and Laboratory Tests
Before Vagifem® 10 is administered; the patient should have a complete physical examination including a blood pressure assessment. 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, blood glucose, serum calcium, triglycerides, 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® 10 should be advised to keep their regular medical checkups to assess the need for continuing therapy.

ADVERSE REACTIONS

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

The following adverse reactions have been reported with estrogen/progestin combination in general:

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.

Placebo Controlled Studies

A placebo-controlled comparison study was done in the U.S. and Canada, in which 308 patients were randomized to receive either placebo (N=103) or Vagifem® 10 tablets (N=205). Patients inserted one tablet intra-vaginally each day for the first two weeks, followed by administration of one tablet intra-vaginally twice weekly administration for the remaining 50 weeks. All patients were assessed for vaginal symptoms. Overall, Vagifem® 10 was generally well tolerated; 41 (20%) patients discontinued treatment in the Vagifem® 10 group and 34 (33%) in the placebo group. Adverse events with an incidence of ≥ 1% in the Vagifem® 10 group and greater than those seen in placebo are reported in Table 1 for this placebo-controlled, multicenter trial.

Table 1: Treatment-Emergent Adverse Events with Possible or Probable Relationship Reported at a Frequency of ≥ 1% with Vagifem® 10

	Vagifem® 10 (n=205)		**Placebo (n=103)**	
	n (%)	**e(%)**	**n (%)**	**e(%)**
Cardiac disorders				
Ventricular extrasystoles	2 (1.0)	2 (1.5)	-*	-*
Gastrointestinal disorders				
Diarrhoea	2 (1.0)	2 (1.5)	-*	-*
Abdominal pain	5 (2.4)	5 (3.8)	1 (1.0)	3 (5.5)
Abdominal pain lower	2 (1.0)	5 (3.8)	1 (1.0)	2 (3.6)
General disorders and administration site conditions				
Therapeutic response unexpected	1 (0.5)	4 (3.1)	-*	-*
Infections and infestations				
Cystitis	1 (0.5)	2 (1.5)	-*	-*
Urinary tract infection	3 (1.5)	3 (2.3)	-*	-*
Vaginal candidiasis	3 (1.5)	3 (2.3)	-*	-*
Vaginal infection	2 (1.0)	3 (2.3)	-*	-*
Vulvovaginal mycotic infection	7 (3.4)	7 (5.4)	1 (1.0)	1 (1.8)
Musculoskeletal & connective tissue				
Back pain	2 (1.0)	2 (1.5)	1 (1.0)	1 (1.8)
Nervous system disorders				
Headache	4 (2.0)	4 (3.1)	4 (3.9)	4 (7.3)
Psychiatric disorders				
Anxiety	2 (1.0)	2 (1.5)	-*	-*

	Vagifem® 10 (n=205)		Placebo (n=103)	
Renal and urinary disorders				
Bladder spasm	1 (0.5)	2 (1.5)	-*	-*
Reproductive system and breast disorders				
Uterine spasm	2 (1.0)	2 (1.5)	-*	-*
Vaginal burning sensation	3 (1.5)	3 (2.3)	1 (1.0)	1 (1.8)
Vaginal odour	4 (2.0)	4 (3.1)	-*	-*
Vulvovaginal discomfort	4 (2.0)	4 (3.1)	2 (1.9)	2 (3.6)
Genital discharge	5 (2.4)	6 (4.6)	-*	-*
Vaginal haemorrhage	8 (3.9)	8 (6.2)	2 (1.9)	2 (3.6)
Vaginal discharge	10 (4.9)	12 (9.2)	8 (7.8)	10(18.2)
Vulvovaginal pruritus	12 (5.9)	12 (9.2)	2 (1.9)	2 (3.6)
Skin and subcutaneous tissue disorders				
Rash	2 (1.0)	3 (2.3)	-*	-*

*No events reported
n=number of patients with adverse events
e=number of adverse events

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Gastrointestinal: Abdominal distension; Nausea.
Hepatobiliary disorders: Cholecystitis acute; Cholethiasis
Infections and infestations: Vulvitis
Injury, poisoning and procedural complications: Post procedural hemorrhage
Investigations: Blood pressure increased; Blood urine present; Hepatic enzyme increased; Mammogram abnormal; Smear vaginal abnormal
Musculoskeletal: Muscle spasm; Pain in extremity
Neoplasm benign, malignant and unspecified (including cysts and polyps): Endometrial adenocarcinoma
Nervous system disorders: Dizziness
Psychiatric Disorders: Depression
Renal and urinary disorders: Dysuria
Reproductive system and breast disorders: Atrophic vulvovaginitis
Skin and subcutaneous tissue disorders: Heat rash; Pruritus
Vascular disorders: Hot flush
Vision Disorders: Blepharitis
Weight Increased

Post-Market Adverse Drug Reactions

No data is available.

If adverse symptoms persist, the prescription of HT should be re-considered.

DRUG INTERACTIONS

Overview

As the estrogen in Vagifem® 10 is administered within the vagina and due to the low levels of estradiol absorption, it is unlikely that any clinically relevant drug interactions will occur with Vagifem® 10.

However, the metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St John's Wort (Hypericum Perforatum) may induce the metabolism of estrogens.

Drug-Drug Interactions

No Drug-Drug Interactions with Vagifem® 10 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® 10 have been reported.

Drug-Herb Interactions

No Drug-Herb Interactions with Vagifem® 10 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®10.

The pathologist should be informed that the patient is receiving hormone therapy (HT) 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® 10 may be used in women with or without an intact uterus.

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

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® 10 may occur if the applicator is introduced too high into the vagina. **Women should be shown how to administer Vagifem® 10 correctly.** No incidences of applicator injury were reported in the clinical trials of Vagifem® 10.

Vagifem® 10 (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, general malaise, breast discomfort and bloating or vaginal bleeding.

The dose of estradiol in Vagifem® 10 is very low compared with oral estrogen products.

Treatment of overdose should be symptomatic.

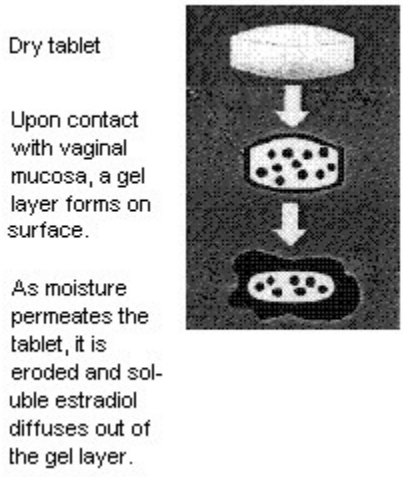
For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Vagifem® 10 (estradiol vaginal tablet) is a hydrophilic, cellulose-derived matrix tablet which hydrates upon contact with moisture, releasing estradiol (Figure 1). The estradiol in Vagifem® 10 is chemically and biologically identical to the endogenous human estradiol and is therefore classified as a human estrogen. Estradiol is the primary estrogen and the most active of the ovarian hormones.

Figure 1. Diffusion of estradiol from a dry vaginal tablet



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 estradiol induces and maintains the primary and secondary female sexual characteristics. Most of the activities of 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 epithelium 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 firs-pass metabolism. After administration of Vagifem® 10 estradiol is absorbed from the vaginal epithelium.

In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Vagifem® 10 demonstrated a mean estradiol (E2) C_{ave} at Day 83 of 4.64 pg/mL after 12 weeks of treatment. (see Table 2).

Table 2: Values for PK Parameters from Plasma Estradiol (E2) Concentrations

Vagifem® 10 E2 (N=29)					
	Day -1	**Day 1**	**Day 14**	**Day 82**	**Day 83**
$AUC_{(0-24)}$ (pg.hr/mL)[a]	75.65	225.35	157.47	44.95	111.41
C_{ave} (pg/mL)[a]	3.15	9.39	6.56	1.87	4.64

AUC = area under the curve,
C_{ave} = Average plasma concentration,
[a] geometric mean

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® 10 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, at room temperature between 15 - 25° C. Protect from light. Store in original package. Do not refrigerate.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Vagifem® 10 (estradiol vaginal tablet) is a small, white, film-coated tablet containing 10.3 µg of estradiol hemihydrate equivalent to 10µg of estradiol.

Each tablet contains the following inactive ingredients: lactose monohydrate, maize starch, hypromellose, 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® 10 is available in cartons of 18 pre-loaded applicators.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

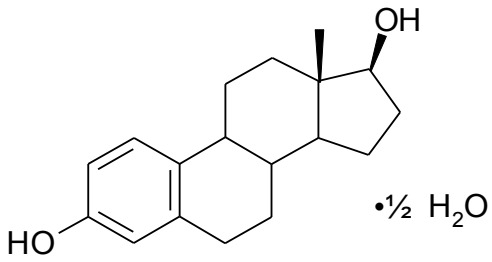
Proper name: estradiol hemihydrate

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

Molecular formula: $C_{18}H_{24}O_2 \bullet ½\ H_2O$

Molecular mass: 281.4

Figure 2: Structural formula



Description: White or almost white crystalline powder or colourless crystals

Solubility: Practically insoluble in water

Melting point: 173 - 179°C

CLINICAL TRIALS

In an open-label, randomised, multiple dose, single-centre trial (VAG-1850) with parallel group design women were treated with either Vagifem® 10 (N=29) or Vagifem® (N=28) for 12 weeks. Vagifem® 10 and Vagifem® were administered daily for 2 weeks, then twice weekly with at least 3 days between each application for the remaining 10 weeks. The purpose of the study was to evaluate the extent of systemic absorption of estradiol during treatment.

Estradiol administered into the vagina at repeated doses of Vagifem® 10 resulted in consistently lower mean plasma concentrations of E2, E1 and E1S than those following administration of Vagifem®. In particular, the average plasma concentration of Estradiol over 24 hours never rose above 20 pg/mL in any of the subjects in the Vagifem® 10 group. C_{ave}(0-24) is a linear transformation of the primary parameter AUC(0-24). In the Vagifem® group, although some subjects had average concentrations above 20 pg/mL especially during the first 14 days of treatment overall, average estradiol concentraions C_{ave}(0-24) remained below 20 pg/mL at all time points. Both treatments were safe and well tolerated.

Efficacy and Safety Studies

Placebo-Controlled Studies

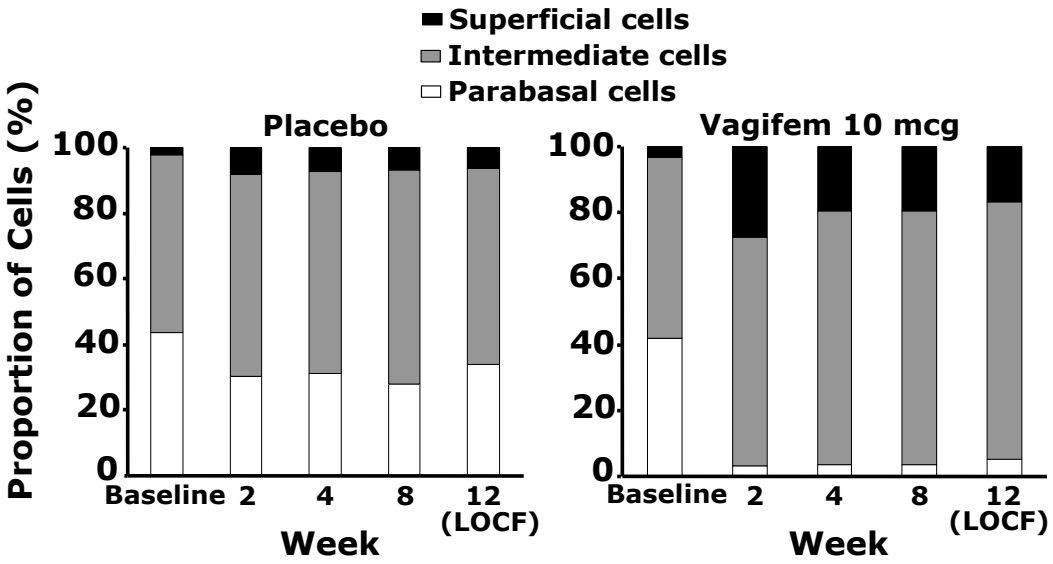
Effect on Vaginal Atrophy

A 12-month double-blind, randomized, parallel group, placebo-controlled study (VAG-2195) was conducted in the U.S. and Canada, in which 308 patients were randomized to receive either placebo or Vagifem® 10 tablets. Patients inserted one tablet intravaginally each day for 14 days, then one tablet twice weekly for the remaining 50 weeks. All patients were assessed for vaginal and urethral cytology, Maturation Value, Vaginal pH, Grading of Vaginal Health, and urogenital symptoms. After 12 weeks of treatment, Vagifem® 10 demonstrated significant improvement superior to placebo in mean score for "Most Bothersome" symptoms, mean Vaginal pH, improvements in Vaginal Maturation Index, Vaginal Maturation Value, and mean Vaginal Health scores. These changes of symptoms were seen at Week 12 and were maintained at Week 52.

Vaginal Maturation Index

At baseline, the proportion of parabasal cells was approximately 43% of the total numbers of cells in both treatment groups. After 2 weeks of treatment the proportion of parabasal cells was <5%, as compared to 30% in the placebo group ($p<0.001$), in the Vagifem® 10 group. In patients treated with Vagifem® 10 the proportion of superficial cells was also increased to approximately 27% after 2 weeks and 17% after 12 weeks (LOCF) from ≤ 5% at baseline ($p<0.001$ at both time points). The mean increase in intermediate cell counts from baseline to Week 12 was approximately 24% ($p<0.001$). (see Figure 3)

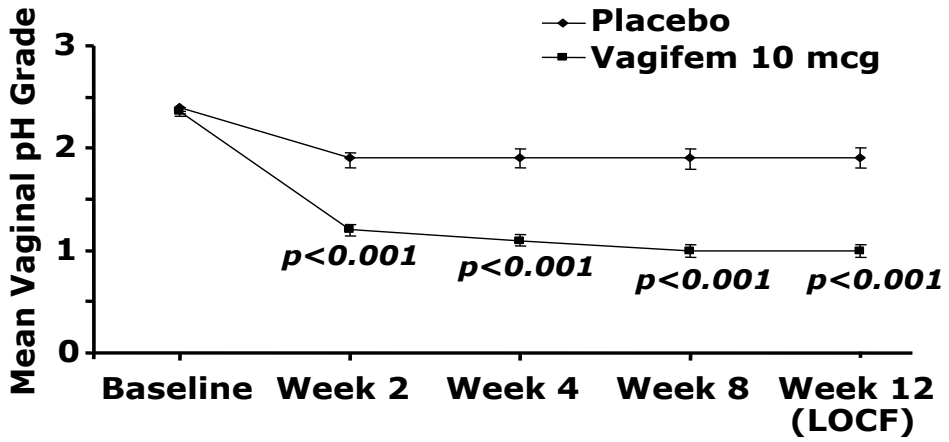
Figure 3: Effect of Placebo and Vagifem® 10 on Vaginal Maturation Index



Vaginal pH

At baseline the majority of subjects in both treatment groups had a vaginal pH ≥ 5.5 (placebo: 91.2%; Vagifem® 10: 82.8%). After 12 weeks of treatment, 71.8% of subjects in the Vagifem® 10 treatment group had a vaginal pH < 5.5, being indicative of a normalization of vaginal pH, as compared to 36.3% in the placebo-treatment group. Mean change from baseline in vaginal pH grade for both treatment groups is presented in Figure 4.

Figure 4: Effect of Vagifem® 10 on Vaginal pH

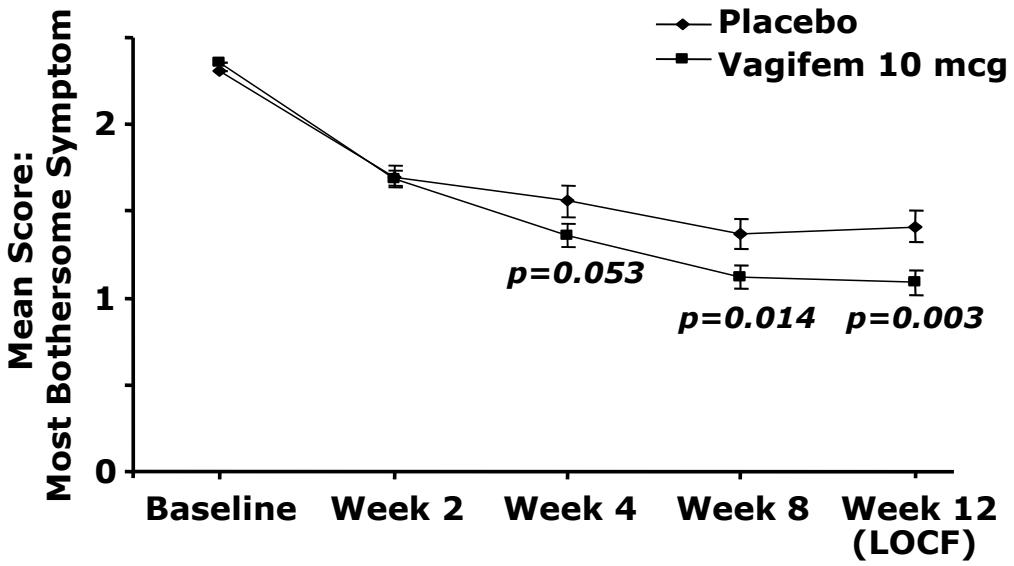


pH < 5 = 0, pH 5 - 5.49 = 1, pH 5.5 - 6.49 = 2, pH > 6.49 = 3

P-values describe comparisons of the change from baseline between treatment groups

Urogenital symptoms
The severity of various symptoms of urogenital atrophy was graded on a 4-point scale as follows: none = 0, mild = 1, moderate = 2, severe = 3. The two symptoms most frequently cited as being "most bothersome" were dyspareunia and vaginal dryness, and these symptoms were usually reported as occurring with moderate to severe intensity. After 8 weeks Vagifem® 10 has shown to be significantly more effective than placebo in the relief of the "most bothersome" symptoms. (see Figure 5)

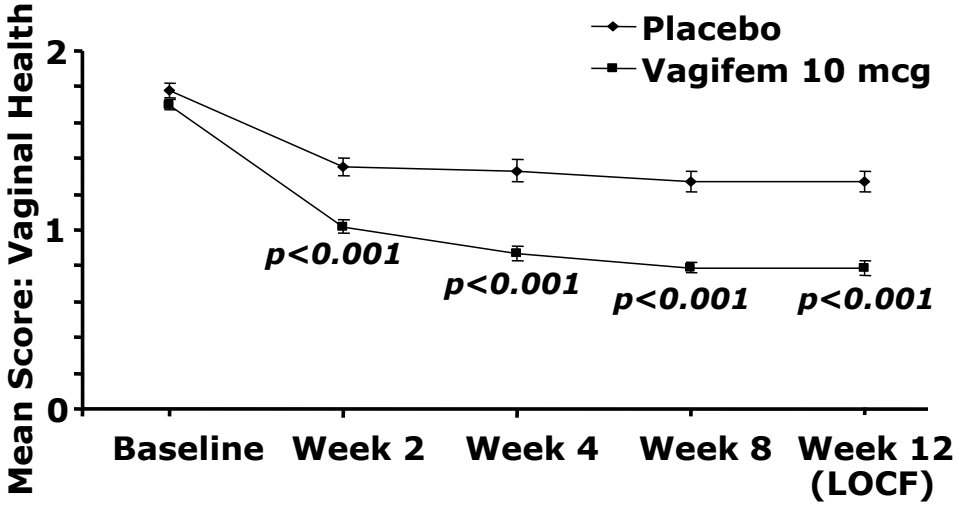
Figure 5: Effect of Vagifem® 10 on "Most Bothersome" Symptoms



P-values describe comparisons of the change from baseline between treatment groups

After 2 weeks of treatment with Vagifem® 10, statistically significant improvement in mean Vaginal Health score was observed and maintained until week 12. Vaginal Health was defined by a four point grading system (no atrophy = 0, mild = 1, moderate = 2, and severe = 3) evaluating five components of Vaginal Health: vaginal secretions, epithelial integrity, epithelia surface thickness, vaginal color and pH. (see Figure 6)

Figure 6: Grading of Vaginal Health with Vagifem® 10 and Placebo Treatment



P-values describe comparisons of the change from baseline between treatment groups

Endometrial Biopsy

The endometrium was evaluated at the screening and final study visits by endometrial biopsy. Of the 172 subjects in the Vagifem® 10 group who had a biopsy performed at end of study, 92 subjects had endometrial tissue that was atrophic/inactive and 73 subjects had no tissue/tissue insufficient for diagnosis. There was one case of adenocarcinoma stage II. The baseline status of this patient was unknown due to lack of a baseline biopsy result. There was one case of complex hyperplasia without atypia, this subject had received study drug for only 9 days prior to this result. Three subjects exhibited polyps (two atrophic polyps and one adenomyomatus type polyp) and two others had adenomyosis and an atypical epithelial proliferation.

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® 10 treatment are not outside the range seen in untreated postmenopausal women. The dosage of 10 µg estradiol in Vagifem® 10 (estradiol vaginal tablet) is low compared to natural production in fertile women and exposure is low compared to other methods of administering estrogen.

After long term maintenance therapy of up to 52 weeks no significant increase in the plasma concentrations of either E_2 or E_1 or E_1S, FSH, LH, or SHBG over baseline were 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® 10.

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® 10
***Estradiol* vaginal tablets**
10 µg
with applicators

This leaflet is Part III of a three-part "Product Monograph" published when Vagifem® 10 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® 10. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Vagifem®10 (estradiol vaginal tablets) is used for the treatment of the symptoms of vaginal atrophy due to estrogen deficiency.

Vagifem® 10 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 therapy (HT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HT.

What it does:
Vagifem® 10 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® 10 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
- Breastfeeding
- Have or have had blood clot disorders, including blood clots in the leg, lung or thrombophlebitis
- Porphyria (a disease of blood pigment)
- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction and/or coronary disease)
- Partial or complete loss of vision due to ophthalmic vascular disease
- Allergy to estradiol or any of the ingredients in Vagifem® 10

What the medicinal ingredient is:
Estradiol hemihydrate

What the important nonmedicinal ingredients are:
Lactose monohydrate, maize starch, hypromellose, magnesium stearate and polyethylene glycol 6000

What dosage forms it comes in:
Vagifem® 10 is available as vaginal tablets, supplied in cartons of 18 vaginal tablets. Each tablet is pre-loaded into the applicator and contains 10 µg estradiol.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at **the lowest effective dose** and for the **shortest period of time** possible. Regular medical follow-up is advised.

Vagifem® 10 is a locally administered vaginal treatment containing 10 µg of estradiol and therefore the occurrence of the conditions mentioned in the box above, is less likely than with estrogen products used for systemic treatment. However, since Vagifem® 10 is a hormone therapy product these risks should be considered.

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 HT.

Women should have a mammogram before starting HT 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.

See your doctor if you notice any changes such as:
- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel

Additionally, you are advised to join mammography screening programs when offered to you. For mammogram screening, it is important that you inform the nurse/healthcare professional who is actually taking the x-ray that you use HT, as this medication may increase the density of your breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

Overgrowth of the lining of the uterus and cancer of the uterus
The use of systemic estrogen-alone therapy by post menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

Vagifem® 10 has not been shown to increase risk of overgrowth of the lining of the uterus and cancer of the uterus.

It is important to report any unusual vaginal bleeding to your doctor right away while you are using Vagifem® 10. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your doctor should check any unusual vaginal bleeding to find out the cause.

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 HT, 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® 10 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 disease called systemic lupus erythematosus for which the most common symptoms are joint pain, skin rash and fever
- 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 high cholesterol or high levels of other fats (such as triglycerides) in the blood
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a condition called otosclerosis that can affect one or both ears and for which the most common symptoms are hearing loss, ringing in the ears and dizziness
- have been diagnosed with diabetes
- are pregnant or may be pregnant
- If you think you may have a vaginal infection

Therapy should be discontinued if any of the following situations is discovered:
- Jaundice or deterioration of liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

INTERACTIONS WITH THIS MEDICATION

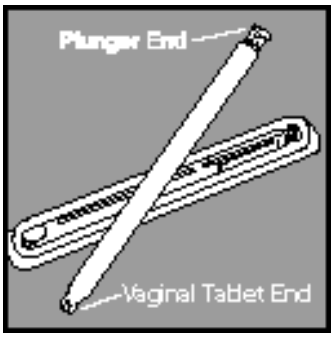
Tell your doctor or pharmacist if you are taking any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

PROPER USE OF THIS MEDICATION

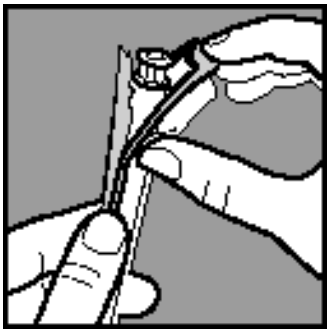
Usual dose:
In order to prevent injury, you need to be shown how to use Vagifem® 10 correctly. Ask your doctor or pharmacist to demonstrate the proper use of Vagifem® 10 applicator.

You can start using Vagifem® 10 on any day of the week at any time of day you like. Once started, it is recommended that Vagifem® 10 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.



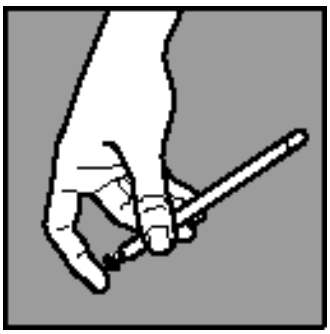
1. Wash your hands.



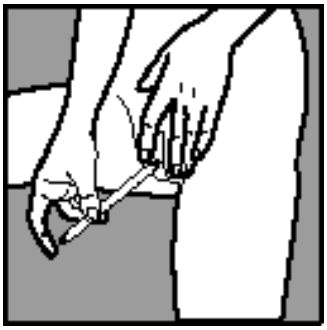
2. Push the Vagifem® 10 applicator through the foil backing (not through the plastic bubble) that says Vagifem®10 and Novo Nordisk.

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.

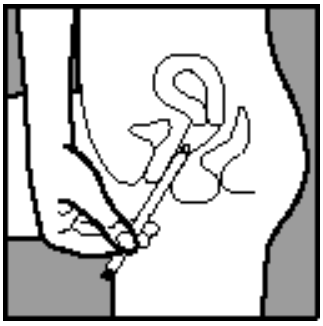
   Inserting Vagifem® 10 is like inserting a tampon.



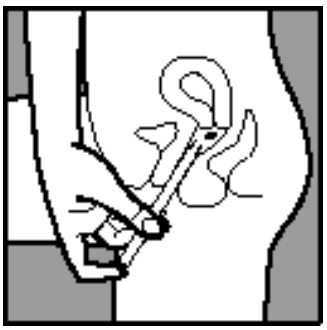
4. Hold the applicator with your thumb and middle finger. Leave your index finger free to press the applicator plunger.



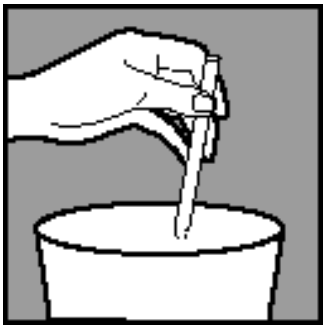
5. With your free hand, hold open the skin at the vaginal opening.



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®10 and Novo Nordisk on the applicator will be outside your body.



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® 10 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.

If you think you have taken too much Vagifem® 10 , contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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 adverse reactions have been reported with estrogen/progestin combination in general:

- Breast edema, breast enlargement, breast pain or pain tenderness
- Peripheral edema (swelling of arms or legs)

The following side effects were reported during clinical trials conducted on Vagifem® 10:

- Genital infection with a fungus or vaginal inflammation
- Headache
- Nausea
- Abdominal pain (stomach), distension or discomfort
- Vaginal bleeding, discharge or discomfort
- Back pain
- Weight gain

Although Vagifem® 10 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.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Abdominal pain, nausea or vomiting		✓	
Unexpected vaginal bleeding		✓	
UNCOMMON			
Allergic reaction: Hives, itching, swelling, low blood pressure (paleness and coldness of skin, rapid heartbeat), sweating			✓
Genital infection with a fungus or vaginal inflammation	✓		
Breast lump		✓	
Heart attack: Crushing chest pain or chest heaviness			✓
Blood clot in the leg (deep vein thrombosis): Leg swelling or pain			✓
Depression: Persistent sad mood			✓
Blood clot in the lungs (pulmonary embolism): Pain in the chest, coughing blood, sudden shortness of breath, or difficulty in breathing			✓
Blood clot in the eye: Sudden partial or complete loss of vision			✓
Stroke: Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in face, arm or leg			✓
Jaundice: Yellowing of the skin or eyes			✓

These are not all the possible side effects of Vagifem® 10. For more information, ask your healthcare provider or pharmacist.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

Keep out of the reach of children. Keep Vagifem® 10 at room temperature, between 15° and 25°C (59 - 77°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.

Do not use Vagifem® 10 after the expiration date printed on the package.

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.novonordisk.ca or by contacting Novo Nordisk Canada Inc., at: 1-800-465-4334

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