PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] pms-ESTRADIOL 10

Estradiol vaginal inserts USP

Vaginal tablet,10 mcg estradiol, vaginal

Vaginal inserts with applicators

Estrogen

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

pms-ESTRADIOL 10 (estradiol vaginal insert USP) is indicated for:

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

1.1 Pediatrics

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

2 CONTRAINDICATIONS

pms-ESTRADIOL 10 (estradiol vaginal insert USP) 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 6 DOSAGE FORMS, STRENGTHS, 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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

pms-ESTRADIOL 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.

4.2 Recommended Dose and Dosage Adjustment

Treatment may be started on any convenient day.

Initial dose:	1 vaginal insert daily for 2 weeks
Maintenance dose:	1 vaginal insert twice a week with a 3 or 4 day interval between doses

4.4 Administration

Accidental injury during administration of pms-ESTRADIOL 10 may occur if the applicator is introduced too high into the vagina. **Women should be shown how to administer pms-ESTRADIOL 10 correctly**. No incidences of applicator injury were reported in the clinical trials of pms-ESTRADIOL 10.

pms-ESTRADIOL 10 (estradiol vaginal insert USP) 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 PATIENT MEDICATION INFORMATION.

4.5 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.

5 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 pms-ESTRADIOL 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
vaginal	Vaginal insert with applicator / 10 mcg estradiol	Hypromellose, lactose monohydrate, magnesium stearate, maize starch and polyethylene glycol 6000

pms-ESTRADIOL 10 (estradiol vaginal insert USP) is a small, white, film-coated insert containing 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol.

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

pms-ESTRADIOL 10 is available in cartons of 18 pre-loaded applicators.

7 WARNINGS AND PRECAUTIONS

pms-ESTRADIOL 10 is a locally administered vaginal treatment containing 10 mcg 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 pms-ESTRADIOL 10 is a hormone therapy product these risks should be considered.

General

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

risks.

pms-ESTRADIOL 10 is a topical, low-dose vaginal estrogen therapy product (see 10.3 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.

Conditions which need Supervision:
The pharmacokinetic profile of Estradiol 10 mcg shows a very low absorption of estradiol during treatment (see 10.3 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

pms-ESTRADIOL 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.

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 2 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 pms-ESTRADIOL 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 pms-ESTRADIOL 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 pms-ESTRADIOL 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 Estradiol 10 mcg.

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 pms-ESTRADIOL 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 pms-ESTRADIOL 10. If a vaginal infection develops during the maintenance phase of the treatment, appropriate therapy should be instituted. The next dose of pms-ESTRADIOL 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 pms-ESTRADIOL 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.

Monitoring and Laboratory Tests

Before pms-ESTRADIOL 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 pms-ESTRADIOL 10 should be advised to keep their regular medical checkups to assess the need for continuing therapy.

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.

7.1 Special Populations

7.1.1 Pregnant Women

Estrogen should not be used in pregnancy. Any possibility of pregnancy must be ruled out before prescribing pms-ESTRADIOL 10. If pregnancy occurs during pms-ESTRADIOL 10 treatment, the medication should be discontinued immediately.

7.1.2 Breast-feeding

Estrogens should not be used when breastfeeding. pms-ESTRADIOL 10 should not be prescribed for nursing mothers.

7.1.3 Pediatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 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.

8.2 Clinical Trial Adverse 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 Estradiol 10 mcg inserts (N=205). Patients inserted one insert intra-vaginally each day for the first two weeks, followed by administration of one insert intra-vaginally twice weekly administration for the remaining 50 weeks. All patients were assessed for vaginal symptoms. Overall, Estradiol 10 mcg was generally well tolerated; 41 (20%) patients discontinued treatment in the Estradiol 10 group and 34 (33%) in the placebo group. Adverse events with an incidence of ≥ 1% in the Estradiol 10 mcg 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 Estradiol 10 mcg

	Estradiol 10 mcg (n=205)		Placebo (n=103)	
	n (%)	e(%)	n (%)	e(%)
Cardiac disorders				
Ventricular extrasystoles	2 (1.0)	2 (1.5)	-*	-*
Gastrointestinal disorders				

	Estradiol 10 mcg (n=205)		Placebo (n=103)	
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)	-*	-*
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

8.3 Less Common Clinical Trial Adverse Reactions

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

8.5 Post-Market Adverse Reactions

In addition to the above-mentioned adverse drug reactions, those presented below have been spontaneously reported for patients treated with Estradiol 10 mcg and are considered possibly related to treatment. The frequencies for the below mentioned adverse drug reactions cannot be interpreted because these reactions are reported voluntarily from a population of uncertain size:

Immune system disorders: Generalized hypersensitivity reactions (e.g. anaphylactic reaction/shock)
Metabolism and nutrition disorders: Fluid retention
Psychiatric disorders: Insommnia
Nervous system disorders: Migraine aggravated
Vascular disorders: Deep vein thrombosis
Skin and subcutaneous tissue disorders: Urticaria
General disorders and administration site conditions: Application site reaction[1], Drug ineffective, Injury associated with device[2]

1Local allergic reactions including Vulvovaginal erythema, Genital erythema, Vulvovaginal rash, Genital rash

2 Minor local trauma caused by intravaginal applicator

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

As the estrogen in pms-ESTRADIOL 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 pms-ESTRADIOL 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.

9.4 Drug-Drug Interactions

No Drug-Drug Interactions with Estradiol 10 mcg have been reported.

See 7 WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

9.5 Drug-Food Interactions

No Drug-Food Interactions with Estradiol 10 mcg have been reported.

9.6 Drug-Herb Interactions

No Drug-Herb Interactions with Estradiol 10 mcg 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.

9.7 Drug-Laboratory Test Interactions

There are no studies investigating Drug-Laboratory interactions with Estradiol 10 mcg.

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

pms-ESTRADIOL 10 (estradiol vaginal insert USP) is a hydrophilic, cellulose-derived matrix insert which hydrates upon contact with moisture, releasing estradiol (Figure 1). The estradiol in pms-ESTRADIOL 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.

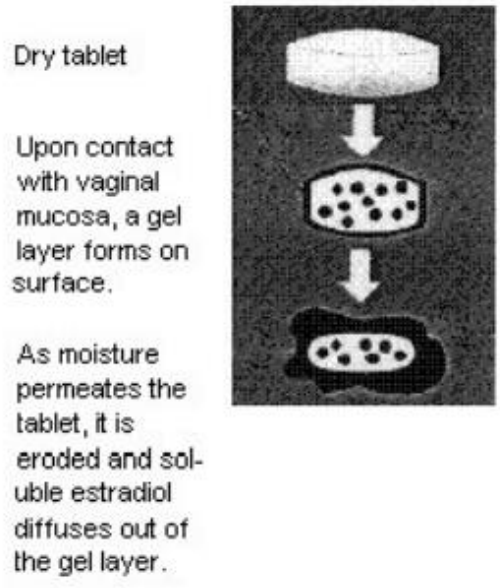


Figure 1. Diffusion of estradiol from a dry vaginal insert

10.2 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.

10.3 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 Estradiol 10 mcg, estradiol is absorbed from the vaginal epithelium.

In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Estradiol 10 mcg 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

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

AUC = area under the curve,
C_{ave} = Average plasma concentration,
1. 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. Estradiol 10 mcg intravaginal administration avoids first-pass metabolism that occurs with oral estrogens.

Elimination:

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

11 STORAGE, STABILITY AND DISPOSAL

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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

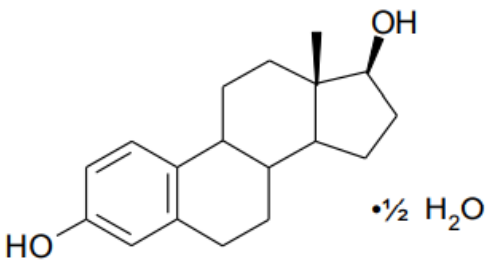
Proper name: estradiol hemihydrate

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

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

Molecular mass: 281.4

Figure 1: Structural formula



Description: White or almost white crystalline powder or colourless crystals

Solubility: Practically insoluble in water

Melting point: 173 - 179°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of the symptoms of vaginal atrophy due to estrogen deficiency

In an open-label, randomised, multiple dose, single-centre trial (VAG-1850) with parallel group design women were treated with either Estradiol 10 mcg (N=29) or Estradiol 25 mcg (N=28) for 12 weeks. Estradiol 10 mcg and Estradiol 25 mcg 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 Estradiol 10 mcg resulted in consistently lower mean plasma concentrations of E2, E1 and E1S than those following administration of Estradiol 25 mcg. In particular, the average plasma concentration of Estradiol over 24 hours never rose above 20 pg/mL in any of the subjects in the Estradiol 10 mcg group. C_{ave}(0-24) is a linear transformation of the primary parameter AUC(0-24). In the Estradiol 25 mcg 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 Estradiol 10 mcg inserts. Patients inserted one insert intravaginally each day for 14 days, then one insert 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, Estradiol 10 mcg 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 Estradiol 10 mcg group. In patients treated with Estradiol 10 mcg 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 2).

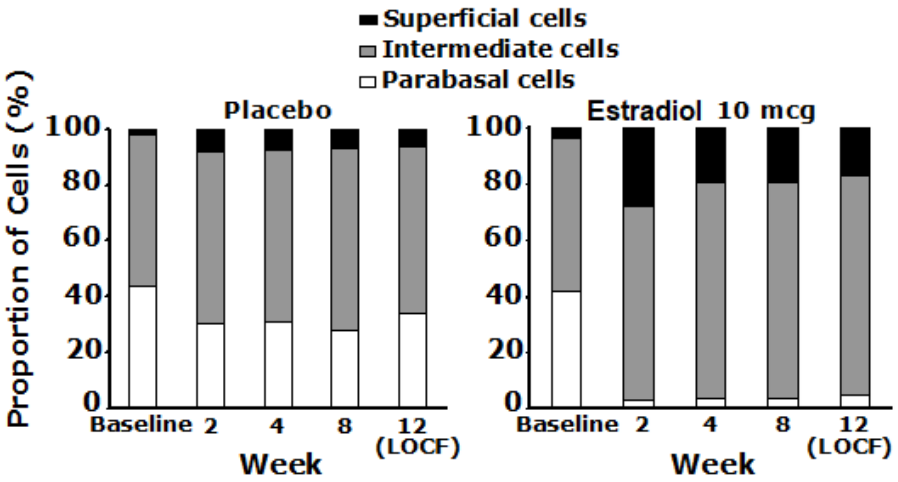


Figure 2: Effect of Placebo and Estradiol 10 mcg on Vaginal Maturation Index

Vaginal pH

At baseline the majority of subjects in both treatment groups had a vaginal pH ≥ 5.5 (placebo: 91.2%; Estradiol 10 mcg: 82.8%). After 12 weeks of treatment, 71.8% of subjects in the Estradiol 10 mcg 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 3.

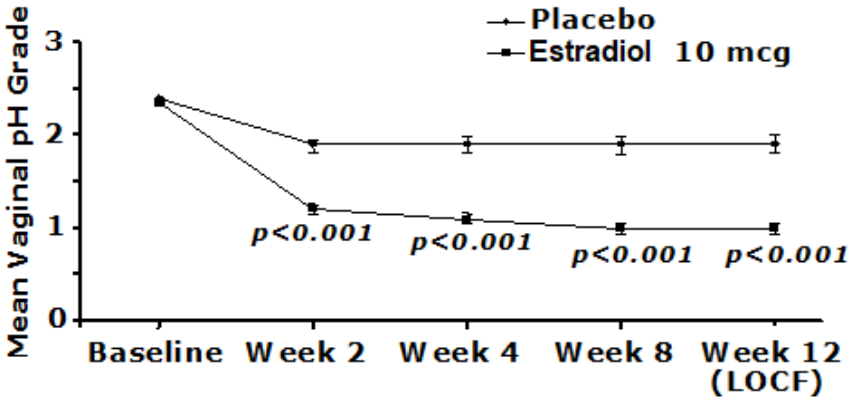


Figure 3: Effect of Estradiol 10 mcg on Vaginal pH

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 Estradiol 10 mcg has shown to be significantly more effective than placebo in the relief of the “most bothersome” symptoms. (see Figure 4).

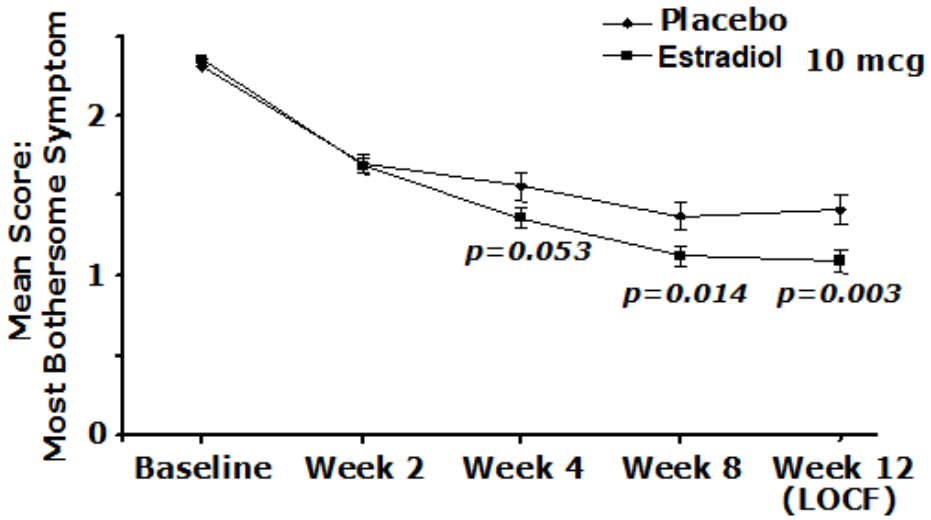


Figure 4: Effect of Estradiol 10 mcg on “Most Bothersome” Symptoms

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

After 2 weeks of treatment with Estradiol 10 mcg, 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 5).

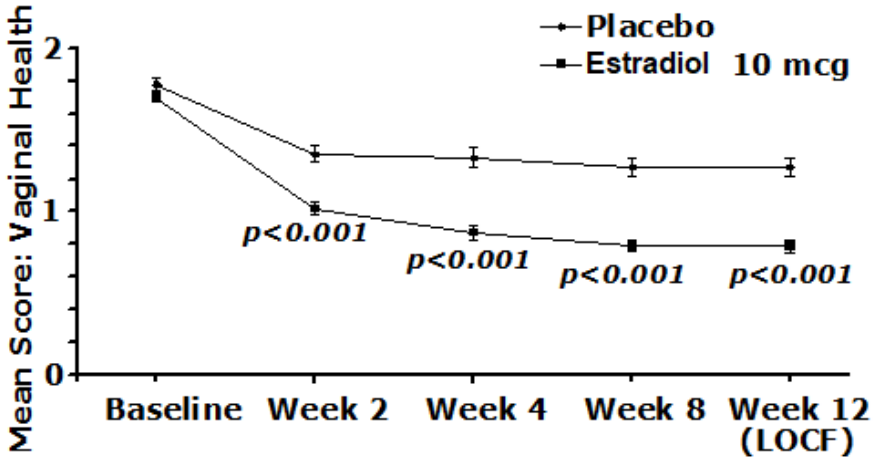


Figure 5: Grading of Vaginal Health with Estradiol 10 mcg and Placebo Treatment

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 Estradiol 10 mg 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Exposure levels to estradiol and estrone following Estradiol 10 mcg treatment are not outside the range seen in untreated postmenopausal women. The dosage of 10 mcg estradiol in estradiol vaginal insert USP 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.

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 insert 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 inserts.

Carcinogenicity:
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 Estradiol 10 mcg.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrVagifem® 10, Estradiol 10 mcg Vaginal tablets with applicators, Submission control number 276051, Product Monograph, Novo Nordisk Canada Inc. NOV 1, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^{Pr}pms-ESTRADIOL 10
***Estradiol* vaginal inserts USP**
10 mcg
with applicators

Read this carefully before you start taking **pms-ESTRADIOL 10** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your doctor or pharmacist about your medical condition and treatment and ask if there is any new information about **pms-ESTRADIOL 10**.

Serious Warnings and Precautions

In postmenopausal women taking oral estrogen-alone, who had a prior surgery removal of the uterus (called a hysterectomy), there is an increased risk of:

- stroke and blood clots in the large veins (**deep vein thrombosis**).

Estrogens with or without progestins should:

- NOT be used for the prevention of heart disease or stroke.
- be used at the **lowest effective dose** and for the **shortest period of time** possible. You should have regular medical check-ups.

What is pms-ESTRADIOL 10 used for?

pms-ESTRADIL 10 is used to treat symptoms of vaginal atrophy due to low levels of estrogen.

How does pms-ESTRADIOL 10 work?

pms-ESTRADIOL 10 provides a sex hormone called estradiol, which is a type of estrogen, to the vagina. This may help reduce dryness and discomfort around your vagina. After menopause, your body makes less or no estrogen. pms-ESTRADIOL 10 replaces the estrogen that are missing in some women.

What are the ingredients in pms-ESTRADIOL 10?

Medicinal ingredients: Estradiol (as estradiol hemihydrate)

Nonmedicinal ingredients: Hypromellose, lactose monohydrate, magnesium stearate, maize starch and polyethylene glycol 6000

pms-ESTRADIOL 10 comes in the following dosage forms:

Vaginal inserts, each containing 10 mcg estradiol. Each insert is pre-loaded into the applicator.

Do not use pms-ESTRADIOL 10 if:

- You have or might have estrogen-dependent cancers;

- Your uterus lining is thicker than normal (endometrial hyperplasia);
- You have, might have or have had breast cancer;
- You have unexplained or unusual bleeding from the vagina;
- You are or may be pregnant or breastfeeding;
- You have or have had blood clotting problems:
    - deep vein thrombosis (blood clots in big veins);
    - pulmonary embolism (blood clots in the lung);
    - thrombophlebitis (inflammation of a vein caused by a blood clot);
- You have porphyria (blood pigment disease);
- You have or had liver problems. This includes blood tests showing your liver is not working properly;
- You have or had a heart attack, stroke, a blockage or narrowing of the arteries around the heart (called coronary heart disease);
- You have eye problems that are caused by low blood flow to the eye;
- You are allergic to estradiol or any of the ingredients in this drug or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-ESTRADIOL 10. Talk about any health conditions or problems you may have, including if you:

- have a history of allergy or intolerance to any drugs or other substances;
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer;
- had any vaginal bleeding that is not normal;
- have or had uterus problems:
    - Fibroids (growths) inside your uterus
    - Endometriosis (growth of the uterine lining outside your uterus)
    - A history of endometrial hyperplasia (overgrowth of the lining of the uterus);
    - have had a hysterectomy (surgical removal of the uterus).
- have a history of liver problems, jaundice (yellowing of the eyes and/or skin) or itching;
- have a history of migraine headache;
- have a disease called systemic lupus erythematosus, an autoimmune disease;
- have high calcium in the blood as a result of kidney disease or cancer;
- have or had high blood pressure;
- have symptoms of blood blockage to the brain;
    - migraine, headaches, trouble speaking, paralysis, loss of consciousness.
- have a history of high cholesterol or high levels of other fats (such as triglycerides) in the blood;
- have or have a history of kidney disease;
- have or have a history of asthma;
- have or have a history of epilepsy (seizures);
- have otosclerosis, an ear problem;
- have been diagnosed with diabetes;
- if you think you may have a vaginal infection;
- smoke.

Other warnings you should know about:

pms-ESTRADIOL 10 has benefits and risks. Consider them when deciding to start taking pms-ESTRADIOL 10 or to carry on taking it. You should talk with your healthcare professional regularly about whether you still need treatment with hormone therapy (HT).

Breast Cancer: For breast cancer, there is:
- An increased risk of breast cancer in postmenopausal women taking combined estrogen plus progestin.
- No difference in the risk of breast cancer in postmenopausal women with a previous hysterectomy taking estrogen-alone.

If you have or had breast cancer, you should not take estrogens with or without progestins.

If you have a family history of breast cancer or have had breast lumps, breast biopsies or abnormal mammograms (breast x-rays), talk to your healthcare professional before starting HRT.

You should have regular breast exams done by your healthcare professional and by yourself. You should review technique for breast self-exams with your healthcare professional. See your healthcare professional if you notice any changes such as:
- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel

You should have a mammogram before starting HT and at regular intervals during treatment. You should join mammography screening programs. For mammogram screening, it is important that you inform the healthcare professional who is taking the x-ray that you use HT. 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 increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus). The risk of endometrial cancer (cancer of the lining of the uterus) increases the longer you use estrogen alone. These risks apply to post-menopausal women with a uterus.

pms-ESTRADIOL 10 has not been shown to increase risk of overgrowth of the lining of the uterus and cancer of the uterus.

Talk to your healthcare professional about the risk factors for overgrowth and cancer of the uterus lining. They should discuss ways to reduce the risks, including progestin treatments. You should report any unexpected or unusual vaginal bleeding to your healthcare professional right away while you are using pms-ESTRADIOL 10.

Ovarian Cancer:
- Women who take estrogen alone or combined HRT for 5 or more years have a slightly higher chance of ovarian cancer.

Heart Disease and Stroke: There is an increased risk of:
- stroke and coronary heart disease in post-menopausal women taking combined oral estrogen plus progestin.

- stroke in post-menopausal women taking oral estrogen-alone HT. There is no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking oral estrogen-alone.

Abnormal Blood Clotting:
- In postmenopausal women taking combined estrogen plus progestin: there is an increased risk of pulmonary emboli and deep vein thrombosis (blood clots in the lung and in big veins).
- In postmenopausal women, with previous hysterectomy, taking estrogen-alone: there is an increased risk of deep vein thrombosis.

You are more likely to get a blood clot in your veins as you get older. Talk to your healthcare professional if any of the below situations apply to you. Blood clots can be life-threatening or cause serious disability if:
- You use estrogens;
- You are unable to walk for a long time because of a major surgery, injury or sickness;
- You are overweight and your BMI is greater than 30;
- You have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- Any of your close relatives has ever had a blood clot in the leg, lung or another organ;
- You smoke;
- You have systemic lupus erythematosus (an autoimmune disease);
- You have cancer.

If you are going to have a surgery, tell your healthcare professional that you are taking pms-ESTRADIOL 10. You may need to stop taking pms-ESTRADIOL 10 at least 4 weeks before the surgery to reduce the risk of a blood clot. Ask your healthcare professional when you can start taking pms-ESTRADIOL 10 again.

Gallbladder Disease:
- The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease that needs surgery.

Dementia (loss of memory and intellectual function):
- There is an increased risk of dementia in women age 65 and older who are taking combined oral estrogen plus progestin.

Physical exam, tests, and check-ups:

- Before you start taking pms-ESTRADIOL 10, your healthcare professional should:
    - Do a physical exam, a Pap smear and a breast exam
    - Do blood pressure tests, blood tests and a mammogram (breast x-ray).
    - Ask you about your personal and your family's health history.
- Your healthcare professional may take samples of your uterus tissue if needed.
- While you are taking pms-ESTRADIOL 10, check your breasts often and get regular check-ups with your healthcare professional.
- Your first check-up should be within 3 to 6 months of starting pms-ESTRADIOL 10. Thereafter, these should be scheduled at least once a year. These check-ups will help to detect any side effects you may have. Your visits may include:
    - a blood pressure check, a breast exam, a Pap smear, pelvic exam, mammograms and blood tests. Your healthcare professional will decide when these are necessary

and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

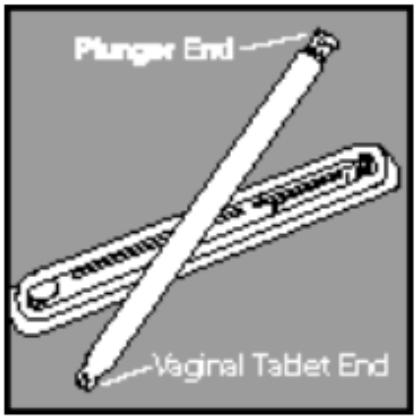
The following may interact with pms-ESTRADIOL 10:

- Medicines that impact liver enzymes;
- Phenobarbital, phenytoin, carbamazepine, used to treat epilepsy and seizures;
- Ritonavir and nelfinavir, used to treat HIV/AIDS;
- Anti-infective medicines such as rifampicin, rifabutin, nevirapine, efavirenz;
- St. John's Wort, used to treat depression.

How to take pms-ESTRADIOL 10:

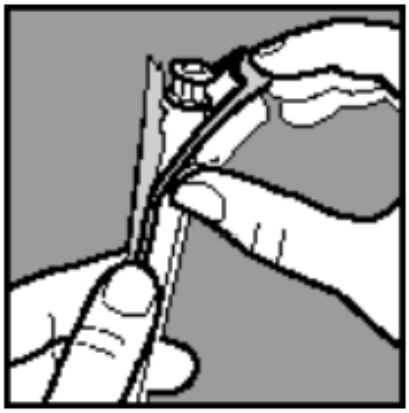
- Ask your healthcare professional to show you how to use the pms-ESTRADIOL 10 applicator.
- Use pms-ESTRADIOL 10 exactly as directed by your healthcare professional.
- Do not use more than the recommended dose prescribed by your healthcare professional.
- Do not change the dose or schedule unless your healthcare professional tells you to.
- pms-ESTRADIOL 10 is a vaginal insert that you place in your vagina.
- **Do not take pms-ESTRADIOL 10 by mouth (orally).**

Steps:



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

1. Wash your hands.

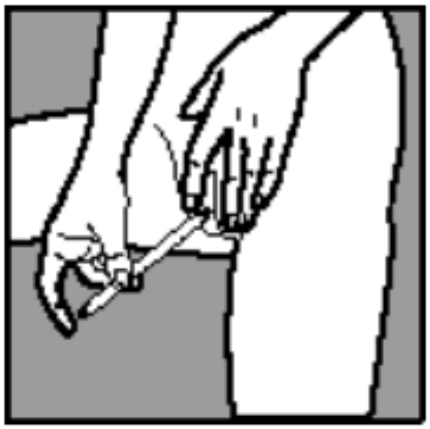


2. Push the pms-ESTRADIOL 10 applicator through the foil backing (not through the plastic bubble) that says pms-ESTRADIOL 10 and Pharmascience Inc.

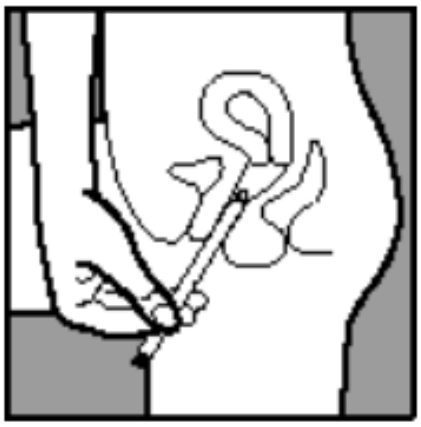
3. Choose the position that is most comfortable for you. You may want to:
   - sit on the edge of a chair with your knees apart,
   - stand up with one foot raised on the edge of the tub or bed,
   - squat,
   - lie down.

   Inserting pms-ESTRADIOL 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.

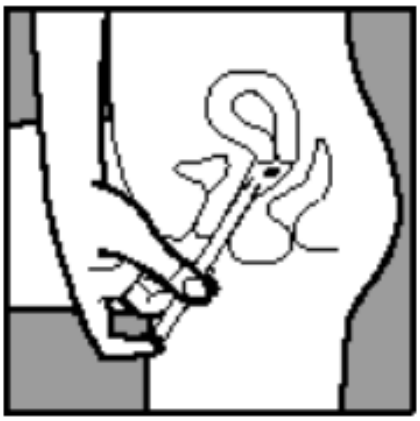


5. With your free hand, hold open the skin at the vaginal opening.



6. Gently slide the vaginal insert 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.



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

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

If pms-ESTRADIOL 10 comes out right after use, it is recommended to insert another vaginal insert.

Recommended Adult Dose:

- Initial dose: 1 vaginal insert daily for two weeks.
- **Maintenance dose:** 1 vaginal insert every three or four days between doses (2 vaginal inserts per week).

Overdose:

Signs of overdose may include feeling sick or vomiting, breast pain, swelling, bloating, cramps, headache, dizziness, general ill feeling or vaginal bleeding.

If you think you, or a person you are caring for, have taken too much pms-ESTRADIOL 10, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed dose:

- If you forget to use a vaginal insert, use one as soon as you remember. However, if the dose is close to the next scheduled dose, skip the missed insert and continue with your next scheduled insert.
- Do not use two vaginal inserts to make up for a missed dose.

What are possible side effects from using pms-ESTRADIOL 10?

These are not all the possible side effects you may feel when taking pms-ESTRADIOL 10. If you experience any side effects not listed here, contact your healthcare professional.

- Breast edema, breast enlargement, breast pain or pain tenderness
- Peripheral edema (swelling of arms or legs)
- Genital infection with a fungus or vaginal inflammation
- Headache, dizziness
- Nausea
- Diarrhea
- Feeling tired
- Abdominal pain (stomach), distension or discomfort
  Vaginal bleeding, discharge or discomfort
- Back pain
- Weight gain
- Acne, rash, itchy skin
- Muscle spasms, pain in extremities
- Anxiety, trouble sleeping

pms-ESTRADIOL 10 can cause abnormal blood test results. Your healthcare professional will decide when these are necessary and will interpret the results. They will tell you if your test results are abnormal and if you need treatment.

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gastrointestinal problems: Abdominal pain, nausea or vomiting		✓	
Palpitation (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): Pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding, severe vaginal bleeding		✓	
UNCOMMON			
Allergic reaction: Hives, itching, swelling, low blood pressure (paleness and coldness of skin, rapid heartbeat), sweating			✓
Application Site reaction around vagina: itching, burning, redness, swelling, rash, or discharge from the vagina, injury from applicator		✓	
Blood clot in the eye: Sudden partial or complete loss of vision			✓
Breast abnormalities (including breast cancer): dimpling or sinking of the skin, changes in the nipple, or any lumps you can see or feel		✓	
Cholestasis (decrease in bile flow from the liver): jaundice (yellowing of the skin or whites of eyes), dark urine, light coloured stools		✓	
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		✓	
Deep vein thrombosis (blood clot in the legs) or **Thrombophlebitis** (inflammation of a vein often in the leg): Leg swelling or pain, redness, warmth, tenderness and pain in affected area			✓
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Heart attack: Crushing chest pain or chest heaviness			✓
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		✓	
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light		✓	
Ovarian cancer: abdominal pain or bloating, quickly feeling full after eating, weight loss, pain in pelvis, change in bowel habits, need to urinate often		✓	
Pulmonary embolism (blood clot in the lungs): Pain in the chest, coughing blood, sudden shortness of breath, or difficulty in breathing			✓
Stroke (blood clot in the brain)**:** Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in face, arm or leg			✓
Urinary tract disorders: difficulty and pain when passing urine, blood in urine		✓	
Vaginal infection (inflammation of the vagina): itching, burning, soreness, odor or discharge from the vagina		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

- Keep out of the reach of children.
- Store in a dry place, between 15° and 25°C. Protect from light. Do not refrigerate.

If you want more information about pms-ESTRADIOL 10:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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