MODULE 4: Vagifem®10 Product Monograph

In this module, we will review the Vagifem® 10 Product Monograph. Bolded callout boxes show you the text copied directly from the Product Monograph along with the page number where the text is found.

INDICATION

(pg 3) Vagifem® 10 (estradiol vaginal tablet) is indicated for:
- The treatment of the symptoms of vaginal atrophy due to estrogen deficiency.

The indication for Vagifem® 10 talks about symptoms of vaginal atrophy and is not restricted to post-menopausal women. Although we have not studied the use of Vagifem® 10 in peri-menopausal women, they too can suffer from vaginal atrophy symptoms related to estrogen deficiency.

The Vagifem® 10 indication makes no mention of the need for a progestin for endometrial protection; this is in contrast to the other local estrogen therapies which have the following statement as part of their indication: should be prescribed with an appropriate dose of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma

Estring® has in the indication: The maximum recommended duration of continuous therapy is 2 years.

Estragyn® Vaginal Cream also has in the indication: Estragyn® Vaginal Cream is intended for short term use.

CONTRAINDICATIONS

Health Canada now requires all estrogen hormone therapy products, including local estrogen treatments, to carry all hormone therapy warnings and contraindications of systemic estrogen.

Therefore the following contraindications related to systemic estrogen are found in all local estrogen treatments:
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- 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 arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease).
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis.
- Partial or complete loss of vision due to ophthalmic vascular disease.

**Estragyn®**

Instead of having the following contraindication: *Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer).*

Estragyn® has: *Known or suspected estrogen-dependent or progestin-dependent malignant neoplasia (e.g. endometrial cancer).*

This highlights the need for a progestin with Estragyn®.

Estragyn® also has the following contraindications:

- **Classical migraine**
- **Breastfeeding**
- *The mineral oil found in Estragyn Vaginal Cream is not compatible with the latex rubber found in most condoms.*

**Premarin® - Precaution and warnings for Premarin® includes a warning about latex condoms**

Preliminary studies conducted by the Health Products and Food Branch have demonstrated that Premarin® Vaginal Cream may react with the latex rubber of certain mechanical barrier devices used for prevention of sexually transmitted diseases and pregnancy (diaphragms and condoms). In additional studies, Premarin® Vaginal Cream has been shown to weaken latex condoms. The potential for Premarin® Vaginal Cream to weaken and contribute to the failure of
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.

**Estring®**

Estring® also carries the contraindication for lactation and porphyria.

**Vagifem® 10**

The contraindication on venous thromboembolism contains past history of thrombophlebitis which is not found in the other local estrogen therapy. This was required by the European Union regulators and for consistency it was added to the Canadian product monograph.

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

Vagifem® 10, like Estring®, is also contraindicated in Lactation or Porphyria.

**WARNINGS AND PRECAUTIONS**

Vagifem® 10 carries the following boxed WHI warnings at the beginning of the warnings and precautions section:

*Premarin® vaginal cream is also contraindicated in women with:

- Known thrombophilic disorders (e.g., protein C, protein S OR antithrombin deficiency); prothrombin mutation or anticardiolipin antibodies.
- Migraine with or without aura.*

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<tr>
<td>- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active or past thrombophlebitis</td>
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*Vagifem® 10 carries the following box:

**WHI Warnings**

At the beginning of the warnings and precautions section:*

*Vagifem® 10 also carries the contraindication for lactation and porphyria.*
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 replacement therapy product these risks should be considered.

It warns against the use of estrogen for prevention of cardiovascular disease, however because it is a local treatment, Vagifem® 10 would not be used for this indication.

It states that the lowest effective dose of estrogen should be used for the approved indication, thereby supporting the use of Vagifem® 10 as it contains the lowest dose of estrogen of any local treatment (vs. Premarin® Vaginal Cream, Estragyn® vaginal cream and Estring®, refer to Module 1 for estrogen dosage comparison).

It warns that estrogen should be used for the shortest period of time possible. However, vaginal atrophy is a chronic condition which worsens over time, does not go away on its own, and symptoms are likely to reappear if treatment is stopped; therefore, shortest period possible for vaginal atrophy is usually long-term treatment.

After the boxed warning comes a balancing statement that tempers these warnings as they relate to Vagifem® 10.

The boxed warning and the balancing statement also appear in the Vagifem® 10 patient information.

The following important guidance appears right under the above information. The guidance endorses that shortest treatment possible will be measured in years, not months or days, since the recommendation is for annual reassessment of therapy.

As well, it is stated that the remainder of the warnings and precautions are attributed to oral estrogen therapy.
The recommendation for annual re-evaluation of therapy as well as the reassessment of the risk benefit ratio would apply to any chronic treatment; any chronic treatment would only be continued if the benefits outweigh the risks.

Systematic absorption may occur with the use of Premarin® Vaginal Cream. Warnings and precautions associated with oral Premarin® treatment should be taken into account.

**Systemic Estrogen Warnings**

The warnings and precaution section contains all the warnings and precaution observed with *systemic estrogen*. Doctors need to keep in mind that the patient information will also contain all these warnings and precautions. Knowing the origins of these warnings may be helpful to patients as oftentimes women can be scared off when they read the information.

The healthcare provider could use the following information to frame these warnings properly:

*Vagifem® 10 is an estrogen containing hormone replacement therapy product. Vagifem® 10 contains estradiol, an estrogen. The patient information on the product will contain all of the warnings, precautions and adverse event seen with oral forms of estrogens.*

*Vagifem® 10 is a topical, low-dose vaginal estrogen therapy product containing only 10 micrograms of estradiol, therefore the warnings and precautions and adverse events or risks associated with oral estrogen therapy are less likely to occur than with Vagifem® 10.*

*The risks and benefits of treatment with Vagifem® 10 should be reassessed at least annually. Vagifem® 10 should only be continued as long as the benefits outweigh the risk.*

**Important Facts about Warnings & Precautions**

We will highlight a few important facts about these warnings and precautions:

**Breast Cancer**

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.

The use of estrogen alone has not been shown to increase the risk of breast cancer. When Vagifem® 10 is used, the women is receiving estrogen only therapy.
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 uterus using VAGIFEM® 10 alone.

Risk of blood clot formation—Venous thromboembolism/stroke
The risk of blood clot formation with estrogen is dose related the higher the dose the higher the risk. The risk is also believed to be associated with the first-pass metabolism (before going into the blood estrogen and progestin given orally must go through the liver first) of oral estrogen. The first pass effect is believed to activate the coagulation factors. Estrogens given vaginally do not undergo first pass metabolism and therefore will not lead to coagulation factor activation (coagulation factors are essential in the formation of blood clots).

Vagifem® 10 dosing being so low would carry a low risk. Compared with Premarin® Vaginal Cream where the same dose is used orally and vaginally (0.3mg and 0.625mg are doses use orally), Vagifem® 10 uses a dose 50 times lower than the lowest effective dose of estradiol used orally (0.5mg).

Conditions which need Supervision
Systemic estrogen treatment is known to aggravate certain conditions which are listed in this section however here again there is wording as to the risk most likely being lower with Vagifem® 10.

Endometrial hyperplasia & endometrial carcinoma
This section of the Vagifem® 10 product monograph now describes the risk associated with unopposed estrogen and this is one of the places where the recommendation that Vagifem® 10 does not require a progestin is found.

Vagifem® 10 is contraindicated in women who are experiencing bleeding of unknown origin (Contraindication: Undiagnosed abnormal genital bleeding). Therefore investigation of the bleed in these women is beneficial to identify the source of the bleeding as well as rule out a cancer before the start of treatment.
Women previously treated with unopposed estrogen would be at higher risk of developing hyperplasia, since it is duration dependent. Therefore investigation of the endometrium prior to the start of Vagifem® 10 is actually a good thing since it will identify patients who are at higher risk or may already have endometrial issues prior to the start of Vagifem® 10 treatment.

Investigation of vaginal bleeding, in a woman who still has a uterus and who is undergoing unopposed treatment with estrogen, is important since this may be a sign of hyperplasia/carcinoma. Stimulation of the endometrium by estrogen, with or without hyperplasia, will most often cause bleeding.

A progestin is not needed since Vagifem® 10 does not increase the risk of endometrial hyperplasia. Remember the only role of a progestin in hormone therapy is to decrease the risk of hyperplasia in women with an intact uterus taking unopposed estrogen.

**Warning and Precaution Pertinent for Vagifem® 10**

**Vaginal Bleeding**

> (pg 6) 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.

The above is to warn about the possible risk of endometrial cancer and the need for women to report these events to their healthcare provider so they can intervene early to prevent further evolution of the underlying cause (if the bleeding is from the uterus, then the endometrium can be treated to prevent cancer development, see Module 3A for more information). Since the use of Vagifem® 10 is contraindicated in women with undiagnosed vaginal bleeding, this explains the need to have the treatment re-evaluated.

**Applicator Trauma**

> (pg 7) Trauma induced by the Vagifem® 10 applicator may occur, especially in patients with severe vaginal atrophy. After gynecological surgery, any vaginal applicator should be used with caution and only if clearly indicated.

The applicator trauma warning highlights the need to start Vagifem® 10 earlier than when condition is so severe even the insertion of a slim applicator can cause problems.
Vaginal Infection

(pg 7) 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.

The warning about vaginal infection reflects the impact of the change in pH and the normal flora which accompanies vaginal atrophy. In clinical trials, vaginal yeast infection (vulvovaginal mycotic infection and vaginal candidiasis) occurred in 4.8% of patients on Vagifem® 10. The reason Vagifem®10 should be stopped if a vaginal treatment is used is because drug interaction studies have not been done to assess the effects of the Vagifem® 10 tablet on the efficacy of the vaginal yeast infection treatment or the effects of the vaginal yeast infection treatment on Vagifem® 10 treatment. In the absence of data and to avoid possible interactions, stopping Vagifem® 10 treatment makes sense.

ADVERSE REACTIONS

In the Vagifem® 10 product monograph the distinction is made between side effects reported with estrogen/progestin combination in general and the adverse reactions reported with the product.

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

(pg 10) 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.

Most common adverse events with Vagifem® 10

In Table 1 (pg 11), containing the adverse event seen in clinical studies, the adverse events reported in >2% of Vagifem® 10 patients were:

- headache
- abdominal pain
- vaginal infection (includes vaginal infection, vulvovaginal mycotic infection and vaginal candidiasis)
- vaginal discomfort or odor
- vaginal hemorrhage
- vaginal discharge, pruritis.

Pruritis, discharge, odor and discomfort are also symptoms associated with vaginal infection so in some patients, these symptoms may be due to the infection and not Vagifem® 10 treatment. Remember that vaginal infections are very common in post-menopausal women due to the increase in vaginal pH associated with vaginal atrophy; it is not surprising that vaginal infections have been reported with Vagifem® 10 in clinical studies.

**DOSAGE AND ADMINISTRATION**

Under Dosing Considerations there is further support for the use of the lowest effective dose. As well, the target patient population is defined as women with or without a uterus. This is where the minimal absorption observed in the first 2 weeks is mentioned and here again we find the recommendation that a progestin is not needed but this time the reason given is because the levels do not usually exceed post-menopausal levels.

*(pg 14) 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.

The recommended dose for Vagifem® 10 is one tablet daily for two weeks, then one tablet twice a week thereafter.

*(pg 14) 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
ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Vagifem® 10 (estradiol vaginal tablet) is a hydrophilic (dissolves in water), cellulose-derived matrix tablet which hydrates upon contact with moisture, releasing estradiol. The estradiol in Vagifem® 10 is chemically and biologically identical to the endogenous human estradiol and is therefore classified as a human estrogen. It can also be referred to as a bioindetical hormone.

It is important to understand the mechanism of action:

**Figure 1.** Diffusion of estradiol from a vaginal tablet

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

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

**PHARMACODYNAMICS**

This section contains the treatment goals for Vagifem® 10 which are:
- reverse atrophic changes
- relieve symptoms.
It also describes what occurs as the vaginal lining matures and what the optimal pH is for re-establishment of the pre-menopausal bacterial environment.

*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.[1]

**PHARMACOKINETICS**

**Absorption**
Here is the first place where the data from the pharmacokinetic study are presented. Presented are the mean AUC and the mean 24-hour estradiol plasma concentration.

*In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Vagifem® 10 demonstrated a mean estradiol (E2) Cave 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 |
|---|---|---|---|---|
| | Day 1 | Day 14 | Day 82 | Day 83 |
| AUC(0.24) (pg.hr/mL)* | 75.65 | 225.35 | 157.47 | 44.95 | 111.41 |
| C_{ave} (pg/mL)* | 3.15 | 9.39 | 6.56 | 1.87 | 4.64 |

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

**DOSAGE FORMS, COMPOSITION AND PACKAGING**
Each trade carton of Vagifem® 10 contains 18 single-use pre-loaded applicators, which is good for 1 month of initial treatment when prescribed once daily for 2 weeks followed by twice weekly administration, or for 2 months of maintenance treatment with twice weekly administration. As most insurers will reimburse up to a maximum of 100 days’ supply of treatment at a time, some pharmacists may dissemble the cartons when dispensing.
Vagifem® 10 (estradiol vaginal tablet) is a small, white, film-coated tablet containing 10.3μg 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.

**CLINICAL TRIALS**

In this section a summary of the following published study can be found: VAG-1850 = Pharmacokinetic trial = Eugster-Hausmann

Key findings of the pharmacokinetic study are mentioned in this section. This is the second place where data from this study is presented. Whereas in the Pharmacokinetic section, only data on Vagifem® 10 is presented, in this section please note that data on Vagifem® 25 µg is also included. In this section a more descriptive narration of the study is given.

Here they mention that with Vagifem® 10 the average 24 hour estradiol level never went above 20 pg/ml in any patients whereas this was seen in the Vagifem® 25 µg group during the first 14 days of treatment in some patients.

*(pg 19)* 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. Cave(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 concentrations Cave(0-24) remained below 20 pg/mL at all time points. Both treatments were safe and well tolerated.

**Efficacy and Safety Studies**

VAG-2195 = key clinical study = Simon

Key findings on the effects of Vagifem® 10 on vaginal atrophy:
- significant improvement in all measures
- sustainability of the effects on symptoms which would include all the parameters (most bothersome symptom, pH, Maturation Index, Maturation Value, Vaginal Health)
After 12 weeks of treatment, Vagifem® 10 demonstrated significant improvement superior to placebo in mean score for “Most Bothersome” symptom, 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**

Key finding on the vaginal maturation index shows the shift from parabasal toward a more mature cell line, with increases in the intermediate and superficial cells and a decrease in the proportion of parabasal cells.

**(pg 19)** 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).

**Vaginal pH**

**(pg 20)** At baseline the majority of subjects in both treatment groups had a vaginal pH higher than or equal to 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 only 36.3% in the placebo-treatment group. Mean change from baseline in vaginal pH )grade pH < 5 = 0, pH 5 - 5.49 = 1, pH 5.5 - 6.49 = 2, pH > 6.49 = 3) in Figure 4.

The figure shows that compared to placebo treatment with Vagifem® 10 leads to a significant change in vaginal pH starting at 2 weeks of treatment and the change is maintained out to week 12 as well as in the long-term (i.e. until week 52).

**Urogenital Symptoms**

Key findings: At baseline, the most bothersome symptom were moderate to severe in intensity as demonstrated by the mean symptom score being between 2 and 3.

At 4 weeks, the effect of Vagifem® 10 on most bothersome symptom is better than placebo (just shy of statistical significance p<0.05) and the effect is significantly different from placebo at 8 and 12 weeks.
Endometrial Biopsy

(pg 22) 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 adenomyomatous type polyp) and two others had adenomyosis and an atypical epithelial proliferation.

Presented here are the endometrial safety results from the key clinical study VAG 2195 only.

These results include all abnormalities found in the study.

One case of Adenocarcinoma stage II (as per the information given in module 2)
A Stage II endometrial adenocarcinoma was diagnosed after 46 weeks of treatment.
- No baseline data was available for this patient due to there not being enough tissue for diagnosis.
The baseline biopsy was not repeated and the patient was enrolled into the study even though this went against the protocol.

It would take longer than 1 year to develop a stage II adenocarcinoma; this is supported by the fact that in a clinical trial lasting for 1 year endometrial safety uses endometrial hyperplasia as an endpoint since hyperplasia is a precursor to carcinoma.

**One case of complex hyperplasia without atypia, this subject had received study drug for only 9 days prior to this result.**

- Development of hyperplasia is related to the dose and the length of treatment.
- Development of hyperplasia related to hormone treatment would take at least months to develop. This is supported by the fact that in the open label endometrial safety study, only patients who had undergone at least 3 months of treatment underwent an end of study biopsy.
- Therefore this case of hyperplasia cannot be considered related to the study drug since it occurred after only 9 days of treatment.

**Three subjects exhibited polyps (two atrophic polyps and one adenomyomatus type polyp)**

- This represents an incidence of 1.7% (3/172).
- Polyps can be present in 13% of asymptomatic postmenopausal women.
- Therefore the rate of polyps with Vagifem® 10 is well below what is seen in this patient population.

**Two others had adenomyosis and an atypical epithelial proliferation**

- These 2 anomalies do not represent risk of cancer.
- Adenomyosis is the presence of endometrial tissue in the muscle layer of the uterus.
- The atypical epithelial proliferation was found in a gland in an atrophic endometrium.