CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020908Orig1s013

Trade Name:	VAGIFEM 10 mcg,
Generic or Proper Name:	estradiol vaginal tablets
Sponsor:	Novo Nordisk Pharmaceuticals, Inc.
Approval Date:	November 25, 2009
Indication:	Vagifem is an estrogen (estradiol) indicated for the treatment of atrophic vaginitis due to menopause.

CENTER FOR DRUG EVALUATION AND RESEARCH

020908Orig1s013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020908/S-013 **SUPPLEMENT APPROVAL**

Novo Nordisk Pharmaceuticals, Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your supplemental new drug application dated and received December 7, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vagifem® (estradiol vaginal tablets) 10 mcg.

We acknowledge receipt of your submissions dated May 26, July 2, September 18, October 30, November 12, 17, 18, and 20, 2009.

Your submission of May 26, 2009, constituted a complete response to our October 15, 2008, action letter.

This supplemental new drug application provides for the use of Vagifem® (estradiol vaginal tablets) 10 mcg for the treatment of atrophic vaginitis due to menopause.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.html that is identical to the enclosed labeling. For administrative purposes, please designate this submission, "**SPL for approved NDA 020908/S-013**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to those submitted October 30, 2009, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or

similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 020908/S-013**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Atrophic vaginitis due to menopause does not occur in pediatric patients.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials and the package insert at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Health Project Manager, at (301)796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SCOTT E MONROE
11/25/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-908/S-013

COMPLETE RESPONSE

Novo Nordisk Pharmaceuticals, Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your supplemental new drug application (sNDA) dated and received December 7, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vagifem® (estradiol vaginal tablets) 10 µg.

We acknowledge receipt of your submissions dated December 7, 2007, January 25, March 27, April 3, 17, 18, May 6, July 25, August 20, 28, September 3, October 1, 2, 3, 6, and 7, 2008.

This supplemental new drug application proposes an indication for (b)(4)

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL AND STATISTICAL ISSUES

Deficiency

Adequate evidence has not been provided to support the effectiveness of Vagifem (estradiol vaginal tablets) 10 µg for the (b)(4) (b)(4). In the analysis of the modified intent-to-treat (m-ITT) population (representing subjects who identified at baseline a moderate to severe most bothersome symptom of VVA, without consideration of their baseline vaginal pH and vaginal cytology), subjects treated with Vagifem (estradiol vaginal tablets) 10 µg did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual moderate to severe symptom of VVA. In the analysis of the m-ITT population as identified in the Agency's advice letter of November 15, 2007 (representing those subjects who identified at baseline a moderate to severe most bothersome symptom and who had a vaginal pH of 5.0 or greater and a vaginal cytology of 5% or less superficial cells), subjects treated with Vagifem (estradiol vaginal tablets) 10 µg also did not demonstrate a statistically significant greater reduction in the severity of at least one individual moderate to severe symptom of VVA, based on an appropriate non-parametric analysis and adjustment for multiplicity.

Resolution of Deficiency

To address the above deficiency, conduct and submit the results of an adequate and placebo-controlled trial to demonstrate the efficacy of Vagifem (estradiol vaginal tablets) 10 µg for the [redacted](b)(4). The trial should enroll subjects with a self-identified moderate to severe most bothersome symptom of VVA due to menopause, a vaginal pH of greater than 5.0, and 5% or fewer superficial cells on a smear from the vaginal wall. The trial should be powered to demonstrate the following at Week 12:

1. A statistically significant improvement over placebo for at least one individual moderate to severe symptom of VVA self-identified by subjects as most bothersome at baseline,
2. A decrease in vaginal pH, and
3. An increase in superficial cells and a decrease in parabasal cells on a smear from the vaginal wall.

If you do not pre-specify the individual moderate to severe most bothersome symptom of VVA that will be investigated, the statistical analysis plan should address the issue of multiplicity. Other details of the trial can be discussed with the Division prior to or at the time of submission of a new protocol.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings with Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call George Lyght, R.Ph., Sr. Regulatory Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Scott Monroe

10/15/2008 04:40:01 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Vagifem safely and effectively. See full prescribing information for Vagifem.

Vagifem® (estradiol vaginal tablets)
Initial U S. Approval: 1999

WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA
See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

Estrogen Plus Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism, and myocardial infarction (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

----------INDICATIONS AND USAGE----------
Vagifem is an estrogen (estradiol) indicated for the treatment of atrophic vaginitis due to menopause (1).

----------DOSAGE AND ADMINISTRATION----------
Vagifem should be administered intravaginally:

- 1 tablet daily for 2 weeks, followed by 1 tablet twice weekly (for example, Tuesday and Friday) (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Vagifem 10 mcg tablet: One vaginal tablet contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol (3)
- Vagifem 25 mcg tablet: One vaginal tablet contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol (3)

----------CONTRAINDICATIONS----------

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active deep vein thrombosis, pulmonary embolism or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction or a history of these conditions (4, 5.2)
- Known liver dysfunction or disease (4, 5.11)
- Known or suspected pregnancy (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- The Vagifem applicator may cause vaginal abrasion (5.17)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

----------ADVERSE REACTIONS----------
In prospective, randomized, placebo-controlled, double-blind studies the most common adverse reactions (incidence ≥5 percent) were upper respiratory tract infection, headache, abdominal pain, back pain, genital pruritis, moniliasis, vulvovaginal mycotic infection and diarrhea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism (7 1)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Women: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.

Revised: 11/2009

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR DISORDERS, ENDOMETRIAL CANCER, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3)]*.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo *[see Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women *[see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2)]*.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Atrophic Vaginitis due to Menopause

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer.

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin *[see Warnings and Precautions (5.3, 5.15)]*.

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

2.2 Recommended Dosing

Vagifem should be administered intravaginally using the supplied applicator: 1 tablet daily for 2 weeks, followed by 1 tablet twice weekly (for example, Tuesday and Friday). Generally, women should be started at the 10 mcg dosage strength.

3 DOSAGE FORMS AND STRENGTHS

Vagifem is a small, white, round, film-coated, bi-convex vaginal tablet containing 10 mcg or 25 mcg of estradiol. Each vaginal tablet is 6 mm in diameter and is administered in a disposable applicator.

4 CONTRAINDICATIONS

Vagifem should not be used in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active deep vein thrombosis, pulmonary embolism or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of these conditions
- Known liver dysfunction or disease
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Risks From Systemic Absorption

Vagifem is intended only for vaginal administration. Systemic absorption occurs with the use of Vagifem. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen therapy should be taken into account.

5.2 Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of pulmonary embolism, DVT, stroke, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogens with or without progestins should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the Women's Health Initiative (WHI) estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted *[see Clinical Studies (14.2)]*. Should a stroke occur or be suspected, estrogens should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg) versus those receiving placebo (18 versus 21 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in all women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to placebo (33 versus 25 per 10,000 women-years) *[see Clinical Studies (14.2)]*. The increase in risk was demonstrated after the first year and persisted.[1]

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal myocardial infarction [MI], silent MI, or CHD death) was reported in women receiving estrogen alone compared to placebo[2] *[see Clinical Studies (14.2)]*.

Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE 0.625 mg compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).[1]

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).[1] An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 *[see Clinical Studies (14.2)]*.

In postmenopausal women with documented heart disease (n=2,763), average age 66.7 years, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]) treatment with daily CE (0.625mg) plus MPA (2.5mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE (0.625 mg) plus MPA (2.5 mg) group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism (VTE)

In the WHI estrogen-alone substudy, the risk of VTE (DVT and pulmonary embolism [PE]) was increased for women receiving daily CE (0.625 mg) compared to placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[3] *[see Clinical Studies (14.2)]*. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted[4] *[see Clinical Studies (14.2)]*. Should a VTE occur or be suspected, estrogens should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

5.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the Women's Health Initiative (WHI) substudy of daily CE (0.625 mg). In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg) was not associated with an increased risk of invasive breast cancer *[relative risk (RR) 0.80]*[5] *[see Clinical Studies (14.2)]*.

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1 24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for estrogen plus progestin compared with placebo.[6] Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for estrogen plus progestin compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups *[see Clinical Studies (14.2)]*.

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent nCI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7] In some epidemiologic studies, the use of estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

5.4 Probable Dementia

In the estrogen-alone Women's Health Initiative Memory Study (WHIMS), an

ancillary study of WHI, a population of 2,947 hysterectomized women aged 65 to 79 years was randomized to daily CE (0.625 mg) or placebo.

In the WHIMS estrogen-alone ancillary study, after an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent nCI, 0.83-2.66). The absolute risk of probable dementia for CE alone versus placebo was 37 versus 25 cases per 10,000 women-years [8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent nCI, 1 21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent nCI, 1.19-2.60). Since both substudies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women [8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

5.5 Gallbladder Disease

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

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.8 Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration or daily with estrogen in a continuous regimen have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.9 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

5.10 Hypertriglyceridemia

In women with preexisting hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.12 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

5.14 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.15 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.16 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

5.17 Local Abrasion

A few cases of local abrasion induced by the Vagifem applicator have been reported, especially in women with severely atrophic vaginal mucosa.

5.18 Laboratory Tests

Serum follicle stimulating hormone and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

5.19 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warning and Precautions (5.2)]*
- Endometrial Cancer *[see Boxed Warning, Warnings and Precautions (5.3)]*

6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a 12-month randomized, double-blind, parallel group, placebo-controlled study, a total of 309 postmenopausal women were randomized to receive either placebo or Vagifem 10 mcg tablets. Adverse events with an incidence of ≥5% in the Vagifem 10 mcg group and greater than those reported in the placebo group are listed in Table 1.

Table 1. Treatment-Emergent Adverse Events Reported at a Frequency of ≥5% and More Frequent in Women Receiving Vagifem 10 mcg

Body System Adverse Event	**Treatment** Number (%) of Women	
	Placebo N = 103 n (%)	**Vagifem** N = 205 n (%)
Body As A Whole		
Back pain	2 (2)	14 (7)
Digestive System		
Diarrhea	0	11 (5)
Urogenital System		
Vulvovaginal Mycotic Infection	3 (3)	17 (8)
Vulvovaginal Pruritis	2 (2)	16 (8)

N = Total number of women in study.
n = Number of women who experienced adverse event.

In a 12-week, randomized, double-blind, placebo-controlled study, 138 postmenopausal women were randomized to receive either placebo or Vagifem 25 mcg tablets. Adverse events with an incidence of ≥5% in the Vagifem 25 mcg group and greater than those reported in the placebo group are listed in Table 2.

Table 2. Treatment-Emergent Adverse Events Reported at a Frequency of ≥5% and More Frequent in Women Receiving Vagifem 25 mcg

Body System Adverse Event	**Treatment** Number (%) of Women	
	Placebo N = 47 n (%)	**Vagifem** N = 91 n (%)
Body As A Whole		
Headache	3 (6)	8 (9)
Abdominal Pain	2 (4)	6 (7)
Back pain	3 (6)	6 (7)
Respiratory System		
Upper Respiratory Tract Infection	2 (4)	5 (5)
Urogenital System		
Moniliasis Genital	1 (2)	5 (5)

N = Total number of women in study.
n = Number of women who experienced adverse event.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post approval use of Vagifem 25 mcg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary System
Endometrial cancer, endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration

Breast
Breast cancer

Cardiovascular
Deep vein thrombosis

Gastrointestinal
Diarrhea

Skin
Urticaria, erythematous/pruritic rash, genital pruritus

Central Nervous System
Aggravated migraine, depression, insomnia

Miscellaneous
Fluid retention, weight increase, drug ineffectiveness, hypersensitivity, blood estrogen increase

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

7 DRUG INTERACTIONS

No drug- drug interaction studies have been conducted with Vagifem.

7.1 Metabolic Interactions

In-vitro and *in-vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Vagifem should not be used during pregnancy *[see Contraindications (4)]*. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Women

Vagifem should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen. Caution should be exercised when Vagifem is administered to a nursing woman.

8.4 Pediatric Use

Vagifem is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Vagifem to determine whether those over 65 years of age differ from younger subjects in their response to Vagifem.

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen-alone substudy (daily conjugated estrogens 0.625 mg versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[see Clinical Studies (14.2)]*.

In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater that 65 years of age *[see Clinical Studies (14.2)]*.

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the estrogen-alone and the estrogen plus progestin substudies when compared to placebo *[see Clinical Studies (14.3)]*.

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [8] *[see Clinical Studies (14.3)]*.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Vagifem has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Vagifem has not been studied.

10 OVERDOSAGE

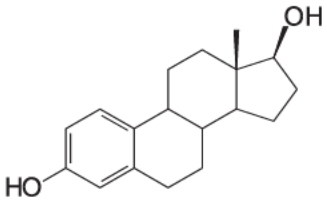
Overdosage of estrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of Vagifem together with institution of appropriate symptomatic care.

11 DESCRIPTION

Vagifem 10 mcg (estradiol vaginal tablets) are small, white, film-coated tablets containing 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol. Vagifem 25 mcg (estradiol vaginal tablets) are small, white, film-coated tablets containing 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol. Each tablet of Vagifem 10 mcg and 25 mcg contains the following excipients: hypromellose, lactose monohydrate, maize starch and magnesium stearate. The film coating contains hypromellose and polyethylene glycol. Each Vagifem tablet is 6 mm in diameter and is placed in a disposable applicator. Each tablet-filled applicator is packaged separately in a blister pack. Vagifem tablets are used intravaginally. When the tablet comes in contact with the vaginal mucosa, estradiol is released into the vagina.

Estradiol hemihydrate is a white, almost white or colorless crystalline solid, chemically described as estra-1,3,5 (10)-triene-3,17β-diol. The chemical formula is $C_{18}H_{24}O_2 \cdot ½ H_2O$ with a molecular weight of 281.4.

The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for Vagifem.

12.3 Pharmacokinetics

Absorption

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

In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Vagifem 10 mcg and 25 mcg demonstrated a mean estradiol (E2) C_{ave} at Day 83 of 5.5 pg/mL and 11.59 pg/mL, respectively after 12 weeks of treatment (see Tables 3 and 4).

Table 3: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters Following Multiple Doses[a] of Vagifem 10 mcg

Uncorrected for baseline, N=29

	E2			E1			E1S		
	AUC_{0-24} (h pg/mL)	$C_{ave\ (0-24)}$ (pg/mL)	%CV[b]	AUC_{0-24} (h pg/mL)	$C_{ave\ (0-24)}$ (pg/mL)	%CV[b]	AUC_{0-24} (h pg/mL)	$C_{ave\ (0-24)}$ (pg/mL)	%CV[b]
Day 1	242 08	10 09	33 02	485 21	20 22	44 86	5158 32	214 93	53 57
Day 14	176 49	7 35	43 69	496 14	20 67	30 88	6323 41	263 48	50 07
Day 83	132 04	5 50	59 69	411 08	17 13	39 58	3804 65	158 53	49 76

[a] Patients received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks
[b] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 4: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters Following Multiple Doses[a] of Vagifem 25 mcg

Uncorrected for baseline, N[c]=28 or 27

	E2			E1			E1S		
	AUC_{0-24} (h pg/ml)	$C_{ave\ (0-24)}$ (pg/ml)	%CV[b]	AUC_{0-24} (h pg/ml)	$C_{ave\ (0-24)}$ (pg/ml)	%CV[b]	AUC_{0-24} (h pg/ml)	$C_{ave\ (0-24)}$ (pg/ml)	%CV[b]
Day 1	495 27	20 64	25 70	567 07	23 63	28 96	5738 32	239 10	47 72
Day 14	466 63	19 44	33 53	662 94	27 62	24 36	7725 90	321 91	43 67
Day 83	278 27	11 59	61 83	500 06	20 84	34 99	4110 84	171 29	51 38

[a] Patients received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks
[b] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[c] N=28 for treatment before Day 14 and N=27 for treatments from Day 14

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Use in Specific Populations

Geriatric Use: There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Vagifem to determine whether those over 65 years of age differ from younger subjects in their response to Vagifem.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of Vagifem has not been studied.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of Vagifem has not been studied.

Drug Interactions

In-vitro and *in-vivo* studies have shown that estrogens are metabolized partially by CYP3A4. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

14 CLINICAL STUDIES

14.1 Effects on Atrophic Vaginitis

Vagifem 10 mcg

A 12-month double-blind, randomized, parallel group, placebo-controlled multicenter study was conducted in the U.S. and Canada to evaluate the efficacy and safety of Vagifem 10 mcg in the treatment of atrophic vaginitis in 309 postmenopausal women between 46 and 81 years of age (mean age = 57.6 years) who at baseline identified their most bothersome symptom of atrophic vaginitis from among six symptoms (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia and vaginal bleeding associated with intercourse). Women inserted one tablet intravaginally each day for 14 days, then one tablet twice weekly for the remaining 50 weeks. The majority (92.9%) of the women were Caucasian (n=287), 3.2 % were Black (n=10), 1.6% were Asian (n=5) and 2.2% were Other (n=7). All subjects were assessed for improvement in the mean change from baseline to Week 12 for co-primary efficacy variables of: a composite of most bothersome symptoms of atrophic vaginitis; percentage of vaginal superficial cells and percentage of vaginal parabasal cells on a vaginal smear; and vaginal pH.

Relief of Vaginal Symptoms

Vagifem 10 mcg was statistically superior to placebo in reducing the severity of a composite score of most bothersome symptoms associated with atrophic vaginitis at Week 12 (see Table 5).

Table 5: Mean Change from Baseline to Week 12 in a Composite Score of Most Bothersome Symptoms Compared to Placebo – ITT Population[a]

	Placebo	Vagifem 10 mcg
ITT Population[a]		
N	93	190
Baseline mean composite score	2.29	2.35
Change from baseline at Week 12 (LOCF)	-0.84	-1.20
p-value versus Placebo	---	0.002

[a] All randomized subjects who received at least one dose of study drug and had at least one post-baseline evaluation.

Also demonstrated for Vagifem 10 mcg compared to placebo was a statistically significant increase in the percentage of superficial cells at Week 12 (13.2 percent compared to 3.8 percent for matching placebo, $p<0.001$), a statistically significant decrease in parabasal cells at Week 12 (-37.0 percent compared to -9.3 percent for matching placebo, $p<0.001$), and a statistically significant mean reduction between baseline and Week 12 in vaginal pH score (-1.3 compared to -0.4 for matching placebo, $p<0.001$).

Endometrial safety was assessed by endometrial biopsy at the screening and final study visit. Of the 172 subjects in the Vagifem 10 mcg group who had a biopsy performed at end of study, 92 subjects had endometrial tissue that was atrophic or inactive and 73 subjects had no tissue or tissue insufficient for diagnosis. There was one case of adenocarcinoma grade 2 and one case of complex hyperplasia without atypia. Three subjects exhibited polyps (two atrophic polyps and one adenomyomatus type polyp) and two others had adenomyosis and an atypical epithelial proliferation.

Endometrial safety of Vagifem 10 mcg was additionally evaluated in a second, 12 month, open-label, multicenter safety study. Of the 297 subjects who had a biopsy performed at end of study, 183 subjects had endometrial tissue that was atrophic or inactive and 111 subjects had no tissue or tissue insufficient for diagnosis. There was one case of complex hyperplasia without atypia. Two subjects exhibited polyps.

Vagifem 25 mcg

A placebo-controlled comparison study was done in the U.S., in which 230 women were randomized to receive either placebo, Vagifem 25 mcg or 10 mcg estradiol vaginal tablets. Women inserted one tablet intravaginally each day for 14 days, then one tablet twice weekly for the remaining 10 weeks. All subjects were assessed for vaginal symptoms. Vagifem 25 mcg was superior to placebo in reducing the severity of a composite score of symptoms associated with atrophic vaginitis (see Table 6).

An open-label, controlled comparison study was done in Canada in which 159 women were randomized to receive either Vagifem 25 mcg or a comparator drug. Two (2) grams of the comparator drug was given daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for up to 24 weeks; Vagifem 25 mcg was administered daily for 2 weeks, then twice weekly for the remaining 22 weeks. In this study, subjects were assessed for relief of symptoms. Vagifem 25 mcg was equally effective as the approved comparator product at the 2.0 gm dose in the relief of symptoms.

Table 6: Mean Change from Baseline to Week 7 and Week 12 in a Composite Score of Symptoms Compared to Placebo – ITT Population[a]

	Placebo	Vagifem 25 mcg
ITT Population[a]		
N	47	91
Baseline mean	1.93	1.85
Change from baseline at Week 7 (LOCF)	-0.85	-1.22
Change from baseline at Week 12 (LOCF)	-0.83	-1.33
p-value versus Placebo – Week 7 (LOCF)	---	0.016
p-value versus Placebo – Week 12 (LOCF)	---	0.005

[a] All randomized subjects who received at least one dose of study drug and had at least one post-baseline evaluation.

In the placebo-controlled study endometrial biopsies in non-hysterectomized women at week 12 were performed on 86 subjects (Vagifem 25 mcg: 32 subjects, estradiol 10 mcg: 33 subjects, Placebo: 21 subjects). Of these, 3 subjects each from the Vagifem 25 mcg and placebo groups and 8 from the 10 mcg estradiol group had insufficient tissue samples. Among those with biopsies that yielded sufficient tissue, results were normal with the exception of one subject in the Vagifem 25 mcg group, who had a simple hyperplasia without atypia.

In the open-label study comparing Vagifem 25 mcg with a comparator vaginal cream on 49 women in each treatment group, endometrial biopsies were obtained at the screening visit and at the end of treatment. At the end of the study (Week 24), all subjects in the Vagifem treatment group whose biopsies yielded sufficient tissue showed an atrophic endometrium with the exception of one subject who had a proliferative endometrium.

14.2 Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These substudies did not evaluate the effects of CE or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints.

Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 years, are presented in Table 7.

Table 7: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI [b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71-1.43)*	*16*	*16*
All Stroke[c]	1.33 (1.05-1.68)	45	33
Ischemic[c]	*1.55 (1.19-2.01)*	*38*	*25*
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[e]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.65(0.45-0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47-0.72)	35	59
Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88-1.32)	53	50
Overall mortality[e,d]	1.04 (0.88-1.22)	79	75
Global Index[g]	1.02 (0.92-1.13)	206	201

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in "global index".
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures.[9] The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality *[see Boxed Warnings, and Warnings and Precautions (5)]*.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined, see Table 7.[10]

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for CHD *[HR 0.63 (95 percent CI, 0.36-1.09)]* and overall mortality *[HR 0.71 (95 percent CI, 0.46-1.11)]*.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 8. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 8: Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs Placebo (95% nCI[c])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53	41	34
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All Strokes	1.31 (1.03-1.68)	33	25
Ischemic stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer[d]	0.81 (0.48-1.36)	6	7
Cervical cancer[d]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures[d]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59-0.85)	44	62
Total fractures[d]	0.76 (0.69-0.83)	152	199
Overall Mortality[f]	1.00 (0.83-1.19)	52	52
Global Index[g]	1.13 (1.02-1.25)	184	165

[a]Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b]Results are based on centrally adjudicated data.
[c]Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d]Not included in "global index".
[e]Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer
[f]All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease.
[g]A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI, 0.44-1.07)]*.

14.3 Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 2,947 predominately healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83 - 2.66).

The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen plus progestin substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years; 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE (0.625 mg) plus MPA (2.5 mg) versus placebo was 2.05 (95 percent CI 1.21-3.48). The absolute risk of probable dementia for CE (0.625 mg) plus MPA (2.5 mg) versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in both the treatment and placebo groups was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women *[see Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

15 REFERENCES

1. Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA*. 2007; 297:1465-1477.
2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med*. 2006; 166:357-365.
3. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006; 166:772-780.
4. Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA*. 2004; 292:1573-1580.
5. Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006; 295:1647-1657.
6. Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA*. 2003; 289:3234-3253.
7. Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic cancers and Associated Diagnostic Procedures. *JAMA*. 2003; 290:1739-1748.
8. Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA*. 2004; 291:2947-2958.
9. Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res*. 2006; 21:817-828.
10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006; 113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Each Vagifem (estradiol vaginal tablets), 10 mcg and 25 mcg, is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contain 8 or 18 applicators with inset tablets.

Vagifem 25 mcg
8 applicators: NDC 0169-5173-03
18 applicators: NDC 0169-5173-04

Vagifem 10 mcg
8 applicators: NDC 0169-5176-03
18 applicators: NDC 0169-5176-04

Keep out of reach of children

16.2 Storage and Handling

Store at 25 C (77 F), excursions permitted to 15 C-30 C (59 F-86 F).
Do not refrigerate.
[See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

See Section 17.5 for FDA-Approved Patient Labeling.

17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.3)]*.

17.2 Possible Serious Adverse Reactions with Estrogens

Inform postmenopausal women of possible serious adverse reactions of estrogen therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

17.3 Possible Less Serious But Common Adverse Reactions with Estrogens

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen therapy such as headache, breast pain and tenderness, nausea and vomiting.

17.4 Instructions for Use of Applicator

Step 1: Tear off a single applicator.

Step 2: Separate the plastic wrap and remove the applicator from the plastic wrap as shown in Figure A.

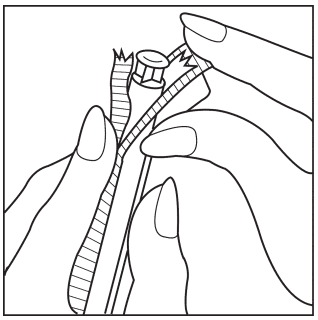


Figure A

Step 3: Hold the applicator so that the finger of one hand can press the applicator plunger as shown in Figure B.

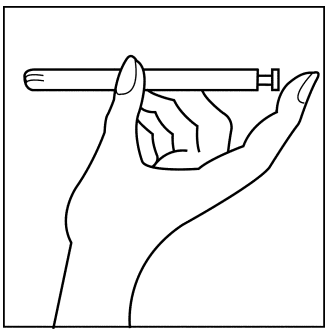


Figure B

Step 4: Next select the best position for vaginal insertion of Vagifem (estradiol vaginal tablets) that is most comfortable for you. See suggested reclining Figure C or standing Figure D position illustrated below:

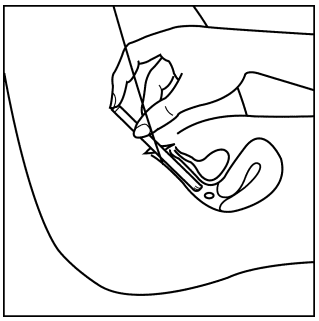


Figure C

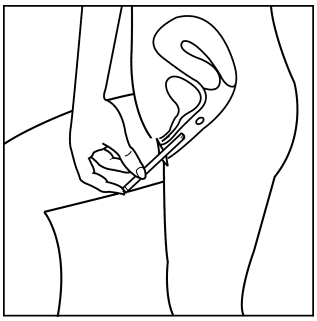


Figure D

Step 5: Using the other hand, guide the applicator gently and comfortably through the vaginal opening (see Figures C and D above). If the tablet has come out of the applicator prior to insertion, do not attempt to replace it. Use a fresh tablet-filled applicator.

Step 6: The applicator should be inserted (without forcing) as far as comfortably possible, or until half of the applicator is inside your vagina, whichever is less.

Step 7: Once the tablet-filled applicator has been inserted, gently press the plunger until the plunger is fully depressed. This will eject the tablet inside your vagina where it will dissolve slowly over several hours.

Step 8: After depressing the plunger, gently remove the applicator and dispose of it the same way you would a plastic tampon applicator. The applicator is of no further use and should be discarded properly. Insertion may be done at any time of the day. It is advisable to use the same time daily for all applications of Vagifem (estradiol vaginal tablets). If you have any questions, please consult your healthcare provider or pharmacist.

17.5 FDA-Approved Patient Labeling

Vagifem® (estradiol vaginal tablets)

Read this PATIENT INFORMATION before you start using Vagifem and read the patient information each time you refill your Vagifem prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms and their treatment.

What is the most important information I should know about VAGIFEM (an estrogen hormone)

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb)

  Report any unusual vaginal bleeding right away while you are using Vagifem. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.

- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline of brain function)

- Using estrogen-alone may increase your chances of getting strokes or blood clots

- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years or older

- Do not use estrogens with progestins to prevent heart disease, heart attack, or dementia

- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots

- Using estrogens with progestin may increase your chance of getting dementia, based on a study of women 65 years and older

- You and your healthcare provider should talk regularly about whether you still need treatment with Vagifem

What is Vagifem?

Vagifem is a medicine that contains estradiol (an estrogen hormone) in a vaginal tablet.

What is Vagifem used for?

Vagifem is used after menopause to:

- Treat menopausal changes in and around the vagina

You and your healthcare provider should talk regularly about whether you still need treatment with Vagifem to control these problems.

Who should not use Vagifem?

Do not start using Vagifem if you:

- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**

  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have, have had or suspect cancer, talk with your healthcare provider about whether you should use Vagifem.

- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Are allergic to Vagifem or any of its ingredients**

  See the list of ingredients in Vagifem at the end of this leaflet.

- **Think you may be pregnant**

Tell your health care provider:

- **If you have any unusual vaginal bleeding**

  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find the cause.

- **About all of your medical problems**

  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **About all the medicines you take**

  This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Vagifem works. Vagifem may also affect how your other medicines work.

- **If you are going to have surgery or will be on bed rest**

  You may need to stop using Vagifem.

- **If you are breast feeding**

  The hormone in Vagifem can pass into your milk.

How should I use Vagifem?

Vagifem is a tablet that you place in your vagina with an applicator.

- Take the dose recommended by your healthcare provider and talk to him or her about how well that dose is working for you

- Estrogens should be used at the lowest dose possible for your treatment only as long as needed

  You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Vagifem.

Step 1: Tear off a single applicator.

Step 2: Separate the plastic wrap and remove the applicator from the plastic wrap as shown in Figure A.

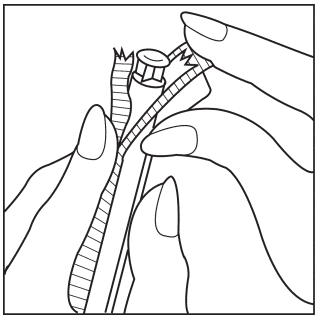


Figure A

Step 3: Hold the applicator so that the finger of one hand can press the applicator plunger as shown in Figure B.

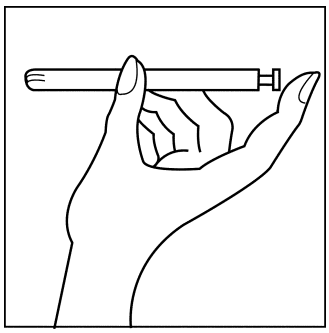


Figure B

Step 4: Next select the best position for vaginal insertion of Vagifem (estradiol vaginal tablets) that is most comfortable for you. See suggested reclining Figure C or standing Figure D position illustrated below:

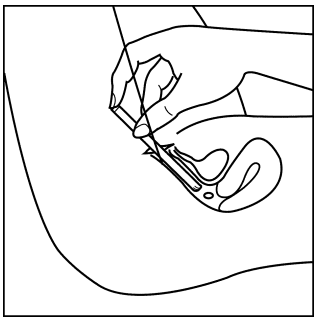


Figure C

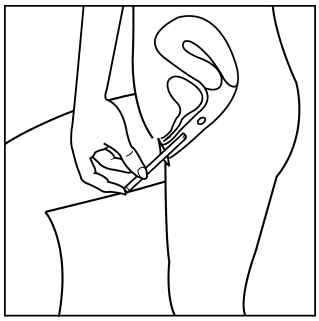


Figure D

Step 5: Using the other hand, guide the applicator gently and comfortably through the vaginal opening (see Figures C and D above). If the tablet has come out of the applicator prior to insertion, do not attempt to replace it. Use a fresh tablet-filled applicator.

Step 6: The applicator should be inserted (without forcing) as far as comfortably possible, or until half of the applicator is inside your vagina, whichever is less.

Step 7: Once the tablet-filled applicator has been inserted, gently press the plunger until the plunger is fully depressed. This will eject the tablet inside your vagina where it will dissolve slowly over several hours.

Step 8: After depressing the plunger, gently remove the applicator and dispose of it the same way you would a plastic tampon applicator. The applicator is of no further use and should be discarded properly. Insertion may be done at any time of the day. It is advisable to use the same time daily for all applications of Vagifem (estradiol vaginal tablets). If you have any questions, please consult your healthcare provider or pharmacist.

Dosage

Vagifem therapy consists of the following dosing regimen:

One (1) Vagifem tablet inserted vaginally once daily for the first two (2) weeks, then one (1) tablet inserted twice weekly (for example Tuesday and Friday) for as long as you use Vagifem.

What are the possible side effects of Vagifem?

Vagifem is only used in the vagina; however, the risks associated with oral estrogens should be taken into account.

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious but less common side effects include:
- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer
- High blood pressure
- Liver problems
- High blood sugar
- Enlargement of benign tumors of the uterus (“fibroids”)

Some of the warning signs of serious side effects include:
- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting
- Yellowing of the skin, eyes or nail beds

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptoms that concern you.

Less serious, but common, side effects include:
- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

These are not all the possible side effects of Vagifem. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with Vagifem?

- Talk with your healthcare provider regularly about whether you should continue using Vagifem

- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you

  The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while using Vagifem.

- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else

If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease

  Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of Vagifem.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Vagifem for conditions for which it was not prescribed. Do not give Vagifem to other people, even if they have the same symptoms you have. It may harm them. **Keep Vagifem out of the reach of children.**

This leaflet provides a summary of the most important information about Vagifem. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Vagifem that is written for health professionals. You can get more information by calling the toll free number 1-888-824-4336.

What are the ingredients in Vagifem?

Vagifem (estradiol vaginal tablets) are small, white, film-coated tablets containing estradiol. Each tablet also contains hypromellose, lactose monohydrate, maize starch and magnesium stearate. The film coating contains hypromellose and polyethylene glycol.

Each Vagifem tablet is contained in a disposable applicator, packaged in a blister pack. Cartons contain 8 or 18 applicators with inset tablets.

Store at 25ºC (77ºF); excursions permitted to 15ºC - 30ºC (59ºF - 86ºF).
Do not refrigerate.
[see USP Controlled Room Temperature].

Vagifem is a trademark owned by Novo Nordisk FemCare AG

Date of Issue: November 2009
Version 5.3

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1-888-824-4336

Manufactured by:
Novo Nordisk A/S
2880 Bagsvaerd, Denmark

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

SUMMARY REVIEW(S)

Summary Review for Regulatory Action

Date	November 25, 2009
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 20-908/S-013 (Complete Response)
Applicant Name	Novo Nordisk, Inc
Date of Submission	May 26, 2009
PDUFA Goal Date	November 26, 2009
Proprietary Name / Established (USAN) Name	Vagifem® Estradiol vaginal tablet
Dosage Forms / Strength	Vaginal tablet / 10 µg estradiol
Proposed Indication	(b)(4)
Proposed Regimen	One intravaginal tablet daily for 14 days followed by one intravaginal tablet twice weekly
Action	***Approve (see Section13.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Theresa van der Vlugt, MD
Statistical Review	Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Alexander Jordan, PhD
CMC Review/ONDQA	Jean Salemme, PhD/Hasmukh Patel, PhD
Microbiology Review	Not needed
Clinical Pharmacology Review	Chongwoo Yu, PhD/Myong-Jin Kim, PharmD
DDMAC	Not needed (class labeling)
DSI (first review cycle)	Jose Tavarez, MS/Constance Lewin, MD
CDTL Review	Shelley Slaughter, MD, PhD
OSE/DMEPA	Jinhee Lee, PharmD/Kellie Taylor, PharmD/Denise Toyer, PharmD
OSE/DRISK	Nancy Carothers/Jodi Duckhorn, MA

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DSI	Division of Scientific Investigations
DRISK	Division of Risk Management
CDTL	Cross-Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objective of NDA 20-908/S-013 is to obtain marketing approval for a lower dosage strength of the currently approved and marketed drug Vagifem® (estradiol vaginal tablets) 25 µg, which contains the equivalent of 25 µg of estradiol per tablet. Vagifem 25 µg was approved in 1999 for the indication of *treatment of atrophic vaginitis*. In the present Application, the Applicant (Novo Nordisk, Inc.) seeks marketing approval for Vagifem (estradiol vaginal tablets) 10 µg (hereafter referred to as Vagifem 10 µg), which contains the equivalent of 10 µg of estradiol per tablet. The proposed dosing regimen for the new lower dosage product is identical to that of the presently marketed product: one intravaginal tablet daily for 14 days with twice weekly dosing thereafter.

NDA 20-908/S-13 initially was submitted on December 7, 2007. The Application was not approved and a Complete Response letter was issued on October 15, 2008. This action was taken because the Applicant's single Phase 3 clinical trial failed to achieve one of 3 co-primary efficacy endpoints in accordance with the 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation." Details of the review issues identified during the first review cycle and the clinical efficacy deficiency are provided in Section 2.2 of the Memorandum. At the post-action meeting between the Division of Reproductive and Urologic Products (DRUP) and the Applicant on March 20, 2009, DRUP and the Applicant discussed possible approaches to resolving the clinical deficiency. In the Meeting Minutes (signed on April 17, 2009), DRUP made the following statements:

- *Based on the discussion and clarification provided by Novo Nordisk, the Division acknowledges that the Applicant may not have fully understood the intent of the draft Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom" prior to the Division's letter of September, 2007.*
- *The Division believes that the clinical deficiency regarding the efficacy of Vagifem (estradiol vaginal tablets) 10 µg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified primary analysis. The Division, however, will need to confirm that the Applicant's composite re-analysis for the most bothersome symptom supports a finding that treatment with Vagifem 10 µg is statistically superior to treatment with placebo*.

On May 26, 2009, the Applicant submitted their Complete Response based on the guidance provided by DRUP. Based on the information provided in the Applicant's Complete Response, both the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application. I concur with their recommendations.

2. BACKGROUND

2.1 Products Available for the Treatment of Atrophic Vaginitis and Vulvar and Vaginal Atrophy

In general, prior to 1999, oral and transdermal estrogen products received approval and class labeling for treatment of atrophic vaginitis and vulvar and vaginal atrophy (VVA) due to menopause as part of their approval for the treatment of vasomotor symptoms (VMS). In most instances, applicants for these oral and transdermal products were not specifically required to conduct an adequate and well-controlled clinical trial specifically for the treatment of symptoms of VVA or atrophic vaginitis due to menopause.

Several vaginal estrogen (estradiol or conjugated estrogens) drug products are currently approved for the treatment of symptoms of VVA or atrophic vaginitis due to menopause. Among these vaginal estrogen products are Premarin® Vaginal Cream (conjugated estrogens cream), Estrace® Cream (estradiol cream), Vagifem® (estradiol vaginal tablets) 25 µg, Estring® (estradiol ring), and Femring® (estradiol ring).

2.2 Regulatory History

In 2003, the Agency issued a draft Guidance for Industry (hereafter referred to as the draft HT Guidance) entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation." The draft HT Guidance recommends that to be considered efficacious for the indication of treatment of VVA, a drug product should be studied in a trial with a population of subjects that display at baseline (1) a moderate to severe symptom of VVA that they describe as most bothersome and (2) physical findings consistent with VVA (i.e., pH $\geq$ 5.0 and < 5% superficial cells on a vaginal smear). To be considered efficacious, products, when compared to placebo, should demonstrate a statistically significant (1) improvement in the subject's most bothersome moderate to severe symptom (i.e., reduction in severity of the symptom), (2) increase in the percentage of vaginal superficial cells, and (3) reduction in vaginal pH.

A detailed chronology of the interactions between the Applicant and DRUP regarding the clinical development program for Vagifem 10 µg is provided in the CDTL Review. The following is a brief overview of these interactions.

The protocol for Phase 3 Study VAG-2195, the primary source of efficacy data for Vagifem 10 µg tablets, was first submitted in October 2004. In a letter dated February 1, 2005, DRUP provided the Applicant with numerous comments and recommendations regarding Study VAG-2195. Among the recommendations was the following statement: "We do not recommend that a composite symptom score, as proposed, be calculated." In September 2007, DRUP recommended to the Applicant that they request a pre-NDA meeting for the Vagifem 10 µg product. The Applicant did not request such a meeting and submitted their supplemental NDA on December 7, 2007. Upon initial review of the Application, it was noted by the primary Clinical Reviewer that the primary statistical analysis for one of the 3 co-primary endpoints (the "most bothersome symptom" of VVA) was based on a composite analysis of all most bothersome symptoms.

Division Director's Comments

- *The draft HT Guidance does not specifically address the issue of the analysis of the most bothersome symptom endpoint. More specifically, it is silent on the acceptability of a composite analysis, based on several symptoms, for this endpoint. For example, a composite endpoint analysis might be based on the overall change in severity of dyspareunia, vaginal dryness, and vaginal irritation. Alternatively, one could interpret the Guidance as requiring that treatment with the proposed drug product demonstrate a statistically better effect than placebo for one or more individual symptoms of VVA (e.g., dyspareunia alone), without consideration of the effect of treatment on other symptoms of VVA.*
- *It was the intent of the principal author(s) of the Guidance that (1) treatment with the proposed drug product demonstrates a statistically better effect than placebo for one or more individual symptoms and (2) a composite analysis of improvement in VVA symptoms would not be an acceptable alternative. Because of this lack of clarity in the draft HT Guidance, Sponsors have been informed at end-of-phase 2 meetings that DRUP does not recommend the use of a composite endpoint for the most bothersome symptom co-primary endpoint.*

The Applicant was requested to modify the primary analysis for this endpoint to conform with the intent of the draft HT Guidance. The Applicant provided the requested analysis, but objected to the request, stating that the protocol and statistical analysis plan for Study VAG-2195 had been designed to investigate the effect of treatment on a composite endpoint and not on one or more or more individual symptoms. Based on DRUP's requested analysis, the primary Clinical Review Team and the Division Director determined that the Applicant had not demonstrated that treatment with Vagifem 10 µg was statistically superior to placebo in terms of improvement in a subject's most bothersome symptom of VVA. Consequently, a Complete Response letter was issued on October 15, 2008, that included the following statement:

> "*Adequate evidence has not been provided to support the effectiveness of Vagifem (estradiol vaginal tablets) 10 µg for* (b)(4) (b)(4) *. In the analysis of the modified intent-to-treat (m-ITT) population (representing subjects who identified at baseline a moderate to severe most bothersome symptom of VVA, without consideration of their baseline vaginal pH and vaginal cytology), subjects treated with Vagifem (estradiol vaginal tablets) 10 µg did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual moderate to severe symptom of VVA. In the analysis of the m-ITT population as identified in the Agency's advice letter of November 15, 2007 (representing those subjects who identified at baseline a moderate to severe most bothersome symptom and who had a vaginal pH of 5.0 or greater and a vaginal cytology of 5% or less superficial cells), subjects treated with Vagifem (estradiol vaginal tablets) 10 µg also did not demonstrate a statistically significant greater reduction in the severity of at least one individual moderate to severe symptom of VVA, based on an appropriate non-parametric analysis and adjustment for multiplicity.*"

Following DRUP's issuance of the Complete Response letter, the Applicant requested and was granted a Type A meeting, which was held on March 20, 2009. At this meeting, the

Applicant stated that they had not understood that their analyses should assess as a co-primary efficacy variable one or more individual moderate to severe individual symptoms of VVA in contrast to a composite of symptoms. The Applicant also stated in the meeting that they had intended that Vagifem 10 µg receive the same indication as that of their approved product Vagifem 25 µg. As stated earlier in Section 1 of this Memorandum, the minutes of the March 20, 2009, meeting stated that "*based on the discussion and clarification provided by Novo Nordisk…the Applicant may not have fully understood the intent of the draft Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom" prior to the Division's letter of November, 2007*." DRUP also stated in the Meeting Minutes that the "*the clinical deficiency regarding the efficacy of Vagifem (estradiol vaginal tablets) 10 µg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified primary analysis…*"

On May 26, 2009, the Applicant submitted their Complete Response that included all of the requested elements described in the minutes of the March 20, 2009, meeting.

2.3 Primary Clinical Reviewer's and Cross Discipline Team Leader's Recommendations regarding Approvability

In the primary Clinical Review for this Application (signed November 20, 2009), Dr. van der Vlugt made the following recommendation and overall assessments:

> *"This reviewer recommends the approval of the 10 mcg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions for the treatment of atrophic vaginitis due to menopause based on the data presented in the Complete Response re-submission for Supplemental NDA 20-908/SE1-013. The re-submission re-analysis of the intent-to-treat (ITT) study population (defined by the Applicant as all randomized subjects who take at least one dose of trial medication and have a baseline and at least one post-baseline efficacy assessment) using last observation carried forward (LOCF) provides sufficient evidence to conclude that the 10 mcg estradiol vaginal tablet demonstrates a statistically significant mean change between baseline and week 12, compared to the placebo vaginal tablet, in a composite of the subject's self-assessed most bothersome symptoms of atrophic vaginitis at baseline (p=0.002). … Vagifem® (estradiol vaginal tablets) 25 mcg was approved on March 26, 1999 for the treatment of atrophic vaginitis based on similar considerations and is currently marketed in the U.S."*

In her CDTL Review for this Application (signed November 20, 2009), Dr. Slaughter made the following recommendations:

> "*I am in alignment with the recommendation that this lower 10 mcg dose of Vagifem® be approved for the treatment of atrophic vaginitis due to menopause, the same indication as the currently approved 25 mcg dose of Vagifem®. I do not recommend granting an indication for* (b)(4) (b)(4)".

Division Director's Comment

- *I concur with the recommendations of Dr. van der Vlugt and Dr. Slaughter that Vagifem 10 µg be approved for the treatment of atrophic vaginitis.*

3. CMC/DEVICE

The primary Chemistry Reviewer, Jean Salemme, PhD, made the following statement in the Conclusions and Recommendations Section of her review (signed September 18, 2008) of the original submission:

> "*Adequate information has been provided to support this supplement. Additionally, the Office of Compliance recommends the proposed manufacturing site for approval. This supplement, therefore, is recommended for approval.*"

The following information is also taken directly from Dr. Salemme's original review:

> *"This efficacy supplement proposes an additional lower strength tablet, 0.010 mg estradiol, to be manufactured at a new drug product manufacturing site, Novo Nordisk in Maaloev, Denmark, with a scale-up in batch size from* (b)(4) *to* (b)(4) *with most of the approved chemistry, manufacturing and controls. The approved methods for identification, assay, related substances, and dissolution have been modified and validated for the analysis of both the 0.025 mg and the 0.010 mg tablets… The data show that the 0.010 mg batches meet the approved drug product specification and are comparable to the approved tablets. The Office of Compliance finds the proposed site acceptable.*"

In her reviews (signed on November 2, 2009, and November 18, 2009) of the Applicant's Complete Response, Dr. Salemme stated the following:

> "*Responses to the Complete Response were submitted 26-May-2009. Revised carton and container labels were submitted 30-Oct-2009. Chemistry review #2 by Dr. Salemme found the revised carton and container labels to be acceptable. …. the responses to the Complete Response did not provide any new CMC information for review*."
>
> "*Therefore, based on the evaluation of the submission as shown in Chemistry review #1, and the evaluation of the revised carton and container labeling as shown in Chemistry review #2, efficacy supplement 20-908 SE2 013 is recommended for Approval from a CMC perspective*."

Division Director Comment

- *I concur with the recommendation for approval made by the primary Chemistry Reviewer. There are no outstanding CMC issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Estradiol is widely used in many products for the treatment of menopausal symptoms. In addition, the composition of Vagifem 10 µg is identical to that of the presently marketed product Vagifem 25 µg, with the exception of a lesser quantity of estradiol (b)(4) (b)(4) In the current Supplement, the Applicant referenced the non-clinical pharmacology/toxicology information contained in original NDA 20-908 for Vagifem 25 µg. Therefore, according to the primary Pharmacology/Toxicology Reviewer, Alexander Jordan, PhD, no new pharmacology, toxicology, or pharmacokinetic/toxicokinetic studies were necessary to support this Application.

Dr. Jordan made the following assessment in his review (signed May 21, 2008) of the original submission:

> *"Based on the approval of Vagifem (estradiol vaginal tablet) 25 μg, which has the same formulation and dosing schedule as Vagifem 10 μg, Pharmacology considers Vagifem (estradiol vaginal tablets) 10 μg safe for the proposed indication.*"

Dr. Jordan made the following recommendation in his review (signed on November 9, 2009) of the Applicant's Complete Response:

> "*The resubmission contains no new pharm/tox information and the original pharm/tox recommendation for approval of Vagifem 10 μg is unchanged*."

Division Director Comment

- *I concur with the recommendation of Dr. Jordan that there are no outstanding nonclinical pharmacology/toxicology issues.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

In addition to the principal safety and efficacy study (VAG-2195), the Applicant also submitted the results of a bioavailability (BA) clinical trial (VAG-1850) in the original Application.

5.1 Study VAG-1850

Study VAG-1850 was a randomized, open-label, multiple-dose, parallel-group, single-center BA study conducted in 58 healthy postmenopausal women with atrophic vaginitis to evaluate the extent of systemic absorption of estradiol (E2) during treatment with Vagifem 10 μg and Vagifem 25 μg. Subjects received one of the 2 treatments. Subjects were treated once daily for the first 2 weeks and a twice weekly thereafter for the following 10 weeks. Table 1 and Table 2 summarize the plasma E2, estrone (E1), and estrone sulfate (E1S) AUC and $C_{ave(0\text{-}24\ hrs)}$ values uncorrected for baseline for the 2 Vagifem products.

Table 1 Arithmetic Means for E2, E1, and E1S PK Parameters during Treatment with Vagifem 10 μg (N=27)

	E2			E1			E1S		
	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both $AUC_{0\text{-}24}$ and $C_{ave(0\text{-}24)}$

Source: Table 1 of primary Clinical Pharmacology Review, signed July 14, 2008.

Table 2 Arithmetic Means for E2, E1, and E1S PK Parameters during Treatment with Vagifem 25 μg (N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Source: Table 2 of primary Clinical Pharmacology Review, signed July 14, 2008.

Chongwoo Yu, PhD, the primary clinical Pharmacology Reviewer, made the following comment in the Executive Summary of his review regarding the pharmacokinetic findings:

> *"E2 administered into the vagina at repeated doses of 10 μg was found to display a PK profile that was globally similar in patterns to that following 25 μg administration. Mean plasma concentrations of E2, E1, and E1S were consistently lower for the Vagifem 10 μg tablet than the currently-marketed Vagifem (25 μg) formulation. The mean E2 plasma concentrations over 24 hr were always below 11 and 21 pg/ml for Vagifem 10 and 25 μg, respectively, even after 14 days of daily administration. Overall, mean E2 concentrations remained within the normal postmenopausal range in both groups, Vagifem 10 and 25 μg."*

5.2 Clinical Pharmacology Recommendation

Dr. Yu made the following recommendation in his review (signed July 14, 2008) of the original submission:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 20-908 submitted on December 7, 2007 and April 18, 2008. The overall Clinical Pharmacology data submitted to support this NDA are acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language."*

No new Clinical Pharmacology information was submitted in the Applicant's Complete Response. Dr. Yu made the following recommendation in his final review (signed on November 20, 2009) of the Complete Response:

> "*The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 20-908 / S-013 acceptable from a Clinical Pharmacology perspective*."

No phase 4 commitments were recommended.

Division Director's Comment

- *I concur with Dr. Yu's recommendation that the Clinical Pharmacology data are sufficient to support approval of Vagifem 10 μg; there are no outstanding clinical pharmacology issues.*

6. CLINICAL MICROBIOLOGY

The primary Chemistry Reviewer, Dr. Salemme, determined in her original Review that a microbiology consult for Vagifem 10 µg was not necessary. The proposed lower strength product will be subject to the same controls as the currently approved and marketed product.

Division Director Comment

- *I concur with this decision.*

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Clinical Program

The primary source of efficacy data for Vagifem 10 µg was Study VAG-2195 in which subjects were treated with study medication for up to 52 weeks. Study VAG-2195 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 45 sites in the US and 4 sites in Canada. A total of 309 postmenopausal women between 46 and 81 years of age (mean age = 57.6 years) were randomly assigned 2:1 to treatment with either Vagifem 10 µg vaginal tablets or placebo vaginal tablets. The inclusion and exclusion criteria were consistent with those of other clinical trials for the treatment of symptoms of VVA. Subjects inserted one tablet intravaginally each day for 14 days, then one tablet twice weekly for the remaining 50 weeks. The majority (92.9%) of the women were Caucasian (n = 287), 3.2% were Black (n = 10), 1.6% were Asian (n = 5) and 2.3% were other (n = 7).

Of the 309 randomized subjects, 34 subjects (32.7%) in the placebo treatment group and 41 subjects (20.0%) in Vagifem 10 µg treatment group discontinued before Week 52. Four subjects (3.9%) in the placebo treatment group and 11 subjects (5.4%) in the Vagifem 10 µg treatment group discontinued because of an adverse event.

Division Director Comment

- *The percentage of subjects who withdrew because of lack of efficacy was higher in the placebo groups (10.6%) compared to that in the estradiol group (2.9%).*

7.2 Efficacy Assessments and Findings

Subjects identified at baseline their most bothersome symptom of atrophic vaginitis from among 6 symptoms (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia, and vaginal bleeding associated with intercourse).
All subjects were assessed for improvement in the mean change from baseline to Week 12 for the co-primary efficacy variables of (1) a composite score based on each subject's most bothersome symptom of atrophic vaginitis, (2) the percentage of vaginal superficial cells and percentage of vaginal parabasal cells on a smear, and (3) vaginal pH.

7.2.1 Change in Most Bothersome Symptom of Atrophic Vaginitis

The mean changes from baseline to Week 12 (or last observation carried forward [LOCF]) in the composite analysis of subjects' most bothersome symptoms of atrophic vaginitis due to menopause in the Vagifem and placebo treatment groups are shown in Table 3. The improvement (i.e., decrease in severity) in the mean composite score was statistically

significantly greater in the Vagifem group (-1.20) compared to the placebo group (-0.84) (p=0.002).

Table 3 Mean Change from Baseline to Week 12 in a Composite of Most Bothersome Symptoms of Atrophic Vaginitis due to Menopause[A] (Study VAG-2195, ITT Population[B])

Visit	Vagifem 10 µg N=190	Placebo N=93	p-value[C]
Baseline	2.36	2.29	-
Change from Baseline to Week 12 (LOCF)	-1.20	-0.84	0.002

[A] Symptoms were evaluated as 0=none, 1=mild, 2=moderate, or 3=severe.
[B] All randomized subjects who received Study Drug, reported a most bothersome symptom at baseline, and had at least one post-baseline efficacy evaluation. For subjects who withdrew before Week 12, the last post-baseline observation was carried forward (LOCF).
[C] From ANCOVA with treatment effect and baseline values as a covariate in the model.
Source: Modified from FDA Statistical Report, Table 1 (signed November 20, 2009).

7.2.2 Change in Vaginal Cytology and Vaginal pH

In the Vagifem-treated subjects, compared to the placebo-treated subjects (see Table 4), the following statistically significant differences were observed:

1. An increase in the percentage of superficial cells at Week 12 (13.2% Vagifem group compared to 3.8% placebo group, p<0.001)
2. A decrease in the percentage of parabasal cells at Week 12 (-37.0% Vagifem group compared to -9.3% placebo group, p<0.001)
3. A reduction in vaginal pH score at Week 12 (-1.3 Vagifem group compared to -0.4 placebo group, p<0.001)

Table 4 Mean Change from Baseline to Week 12 in Vaginal Cytology (Percent of Parabasal and Superficial Cells) and Vaginal pH Score (Study VAG-2195, mITT Population)

Parameter	Vagifem 10 µg		Placebo		p-value*
	N	Mean Value	N	Mean Value	
Parabasal Cells (%)					
Baseline	198	41.8	102	43.4	
Change [A]	195	-37.0	102	-9.3	<0.001
Superficial Cells (%)					
Baseline	198	3.3	102	2.5	
Change [A]	195	13.2	102	3.8	<0.001
Vaginal pH Score					
Baseline	204	2.3	102	2.4	
Change [A]	202	-1.3	102	-0.4	<0.001

[A] Change from Baseline to Week 12 (or LOCF).
* Significance of change from baseline in Vagifem group vs. placebo group.
Source: Table 3 of FDA Statistical Review, signed November 20, 2009.

7.2.3 Assessment of Efficacy (FDA Statistical Review)

The FDA statistical reviewer, Mahboob Sobhan, PhD, made the following statement in the Conclusions and Recommendations section of his review (signed on November 20, 2009) of the Applicant's Complete Response:

> "*The study results support the efficacy of Vagifem (10 mcg estradiol vaginal tablets) in the treatment of atrophic vaginitis due to menopause. Treatment with Vagifem resulted in a statistically significant reduction in (1) a composite score of all most bothersome symptoms, (2) vaginal pH, (3) the percentage of parabasal cells compared to treatment with placebo at week 12. A statistically significant increase in superficial cells for treatment compared to placebo at week 12 was also demonstrated."*
>
> *"From a statistical perspective, the results demonstrate the efficacy of Vagifem 10 mcg in the treatment of atrophic vaginitis due to menopause*."

7.3 Overall Assessment of Efficacy

In Study VAG-2195, treatment with Vagifem 10 µg was shown to be statistically superior to treatment with placebo tablets for each of the 3 protocol-specified co-primary efficacy endpoints. Treatment with Vagifem 10 µg was statistically superior to treatment with placebo in terms of: (1) reducing the severity of a composite score based on each subject's most bothersome symptom of atrophic vaginitis, (2) improving vaginal cytology (i.e., increasing the percentage of superficial cells and reducing the percentage of parabasal cells), and (3) reducing vaginal pH.

Division Director's Comments

- *In my Memorandum signed on October 14, 2008, at the completion of the first review cycle, I stated that the Applicant had not demonstrated that treatment with Vagifem 10 µg was statistically superior to treatment with placebo, based on an analysis of* ***individual*** *most bothersome symptoms of VVA. I also stated that based on the recommendations of the 2003 draft HT Guidance a composite analysis of most bothersome symptoms was not appropriate or acceptable.*
- *Since the issuance by DRUP of the Complete Response letter in October 2008, I have changed my position regarding the acceptability of a composite analysis for the most bothersome symptom endpoint for this Application for several reasons.*
  1. *Based on the meeting with the Applicant on March 20, 2009, I believe that the Applicant most likely did not understand the intent of the 2003 draft HT Guidance regarding assessment of the most bothersome symptom endpoint. The Applicant's protocol for Study VAG-2195 had prespecified a composite analysis and the sample size was based on a composite endpoint analysis.*
  2. *Vagifem 10 µg is a lower dosage of an approved and currently marketed product (Vagifem 25 µg). Approval of Vagifem 25 µg was based on a composite analysis of symptoms of atrophic vaginitis.*
  3. *The indication for Vagifem 10 µg will be treatment of atrophic vaginitis (a composite endpoint) due to menopause, which is identical to the indication for Vagifem 25 µg. The indication will not be for* (b)(4) (b)(4).

- *I concur with the CDTL that approval of Vagifem 10 µg, based in part on a statistically significant improvement of subjects' most bothersome symptoms of atrophic vaginitis using a composite analysis, should not establish a precedent for other products* (b)(4) (b)(4) *. Rather, the use of a composite analysis would likely be acceptable only in situations where a lower dosage of a previously approved product is being studied.*

8. SAFETY

In her primary Clinical Review (signed on October 6, 2008) of the original submission, Dr. van der Vlugt provided a thorough discussion and review of the safety findings for Vagifem 10 µg. Her primary review was based on: (1) the data provided in the origin submission of NDA 20-908/s-013, (2) the 4-month safety update, and (3) a review by Adrienne Rothstein, PharmD (Office of Surveillance and Epidemiology) of postmarketing safety data in the FDA's Adverse Event Reporting System (AERS) database. The Clinical Team Leader (Dr. Slaughter) also reviewed the safety data provided in the original submission. Neither of these Medical Officers identified any safety issues that would suggest that the overall safety profile for Vagifem 10 µg would be less acceptable than that for other currently approved vaginal estrogen products.

In this Complete Response, the Applicant, at the request of DRUP, submitted additional safety data for Vagifem 10 µg. These data were contained for the most part in the Final Report for Study VAG-1748, which was conducted primarily to obtain additional information regarding the effect of treatment with Vagifem 10 µg on the uterine endometrium. This additional Study has been thoroughly reviewed in the primary Clinical Review (signed on November 20, 2009) of the Applicant's Complete Response.

8.1 Study VAG-2195

One of the 2 primary sources of safety data for Vagifem 10 µg was Study VAG-2195 in which subjects were treated with study medication for up to 52 weeks. Study VAG-2195 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial in which 308 healthy postmenopausal women received study drug. Subjects were randomly assigned 2:1 to treatment with either Vagifem 10 µg or placebo vaginal tablets. One major safety objective of Study VAG-2195 was the evaluation of endometrial safety as assessed by endometrial biopsy at the end of treatment. Other safety assessments included vital signs, physical examination, gynecological examination, papanicolaou cervical smear, transvaginal ultrasound, and monitoring of adverse events.

8.1.1 Deaths and Other Serious Adverse Events

There were no deaths in Study VAG-2195 or in the supportive PK study (Study VAG-1850). In Study VAG-2195, 7 of 308 subjects reported serious adverse events (5/205 [2.4%] subjects in the estradiol treatment group and 2/103 [1.9%] subjects in the placebo group). The 5 serious adverse events in the estradiol treatment group were one case each of ventricular extrasystoles (premature ventricular contractions), acute cholecystitis, pneumonia, infra-orbital squamous cell carcinoma, and endometrial cancer. The 2 serious adverse events in the placebo treatment group were one case each of coronary artery stent occlusion and gastrointestinal hemorrhage.

Division Director Comments

- *Overall, the percentage of subjects reporting serious adverse events in 52-week Study VAG-2195 was low and was similar in the estradiol and placebo treatment groups.*
- *The percentage of subjects reporting serious adverse events and the specific events do not raise any concerns about the overall safety profile of Vagifem 10 µg, other than those associated with all estrogen drug products.*
- *The single case of endometrial adenocarcinoma in the estradiol treatment group in Study VAG-2195 is discussed in Section 8.2.3 (Division Director's Comments).*

8.1.2 Discontinuations for Adverse Events

Fifteen (15) of the 308 subjects who received study drug discontinued prematurely because of an adverse event (11/205 [5.4%] in the Vagifem 10 µg group and 4/103 [3.9%] in the placebo group).

Division Director's Comments

- *Overall, the percentage of subjects who discontinued prematurely was low for a 52-week study for the treatment of atrophic vaginitis; the overall findings do not raise any new safety concerns.*

8.1.3 Common Adverse Events

Adverse events reported in at least 5% of subjects in either treatment group in Study VAG-2195 are listed in Table 5.

Table 5 Common Adverse Events (Reported in ≥ 5% of Subjects) in Study VAG-2195

Adverse Event	Vagifem 10 µg (N=205) n (%)	Placebo Vaginal Tablet (N=103) n (%)
Vulvovaginal mycotic infection	17 (8.3)	3 (2.9)
Vulvovaginal pruritus	16 (7.8)	2 (1.9)
Headache	15 (7.3)	13 (12.6)
Nasopharyngitis	14 (6.8)	7 (6.8)
Back pain	14 (6.8)	2 (1.9)
Vaginal discharge	12 (5.9)	8 (7.8)
Diarrhea	11 (5.4)	0 (0.0)

Source: Modified from Table 27, Primary Medical Review of original submission, Section 7.1.5.3., signed October 6, 2008.

Division Director's Comment

- *The most commonly reported treatment-emergent adverse events in Study VAG-2195 do not raise any new safety issues for an estradiol vaginal product.*

8.1.4 Endometrial Biopsy Findings

All subjects in Study VAG-2195 were to have had an endometrial biopsy performed at screening and at the end-of-study or early termination, provided the subject had been treated for 3 months or longer. Among 79 posttreatment biopsies in the placebo treatment group,

there were no abnormal findings. Among the 172 posttreatment biopsies in the Vagifem treatment group, there was a single case of complex hyperplasia without atypia and a single case of adenocarcinoma.

Division Director's Comment

- *The single case of complex hyperplasia without atypia was not likely secondary to treatment with study drug because the subject was treated for only 9 days. The single case of adenocarcinoma of the endometrium diagnosed after approximately one year of treatment may have been related to estradiol treatment.*

8.2 Study VAG-1748

8.2.1 General Description

Study VAG-1748, which was not included in the original submission, was an open-label, single-arm, multi-center, non-US clinical trial conducted primarily (1) to assess the endometrial safety of the 10 µg estradiol vaginal tablets and (2) to support the registration of the product in Europe. Healthy postmenopausal women with an intact uterus and at least one urogenital symptom of moderate to severe intensity were enrolled. All subjects were treated with 10 µg estradiol vaginal tablets using the same dosing regimen as in Study VAG-2195. All subjects were to have had an endometrial biopsy performed at screening and at the end-of-study or at early termination, provided the subjects had been treated for 3 months or longer.

8.2.2 General Safety Findings

One death was reported in the Study VAG-1748. The death of a 77-year old women was attributed to cerebral metastasis of a primary unknown cancer and was assessed as "unlikely related" to study medication by the investigator and the Applicant.

Based on information in the primary Clinical Review of the Complete Response:

- Forty-four (44) of the 336 subjects (13.1%) who started treatment discontinued prematurely: 18 due to adverse events (5.4%), 7 due to non-compliance (2.1%), 6 due to ineffective therapy (1.8%), and 13 due to other reasons (3.9%).
- Fourteen (14) subjects (4.2%) experienced serious adverse events.

Division Director's Comment

- *The overall safety profile of 10 µg estradiol vaginal tablets in Study VAG-1748 does not raise any safety concerns beyond those associated with the use of all estrogen drug products.*

8.2.3 Endometrial Findings

Of the 336 subjects who had an endometrial biopsy at baseline, 297 (88.4%) had an end of treatment endometrial biopsy. Of these 297 subjects, 183 subjects had endometrial tissue that was atrophic or inactive and 111 subjects had no tissue or tissue insufficient for diagnosis. There was one case of complex hyperplasia without atypia. Two subjects were found to have endometrial polyps.

Division Director's Comments

- *The endometrial biopsy findings from Study VAG-1748 are consistent with those from Study VAG-2195 and do not raise any new safety concerns.*

- *Treatment with estrogen alone is well known to produce endometrial hyperplasia and less frequently endometrial cancer. Because of this risk, class labeling for estrogen products recommends the use of a progestin (continuous or intermittent) in women with a uterus who are treated with an estrogen product. I agree with the recommendations of the primary Clinical Reviewer and the Clinical Team Leader that labeling for Vagifem 10 µg should include the class recommendation regarding the use of a progestin for endometrial protection.*

8.3 Overall Assessment of Safety

The primary Clinical Reviewer made the following summary statement regarding the safety of Vagifem 10 µg in Section 1.3.3 of her original review (signed on October 6, 2008):

> *"The safety data presented in the submission demonstrates an acceptable overall safety profile of the 10 µg estradiol vaginal tablet, administered intravaginally daily for two weeks and then twice-weekly thereafter…The SAEs reported in Study VAG-2195 do not raise safety concerns."*

In her review of the Applicant's Complete Response, which included an additional safety study (Study VAG-1748), the primary Clinical Reviewer made the following statement in Section 1.1 of her review, signed on November 20, 2009:

> "*The safety of the 10 µg estradiol vaginal tablet was not a concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved* (b)(4) (b)(4) ,,

The Clinical Team Leader made the following summary assessment regarding the safety of Vagifem 10 µg on page 15 of her original review (signed on October 10, 2008):

> *"Overall, the safety profile as presented in the integrated summary of safety is acceptable and is not sufficiently different from previously approved estrogen-only products (including the 25 µg dose of Vagifem®) to raise any additional concerns or to not receive class labeling."*

Division Director Comments

- *I concur with the overall assessments of the primary Clinical Reviewer and the Clinical Team Leader that the safety profile of Vagifem 10 µg is acceptable and raises no new concerns for an estrogen vaginal product.*
- *The safety profile for Vagifem 10 µg in general clinical use will likely be comparable to that of other vaginal estrogen drug products approved for the treatment of atrophic vaginitis* (b)(4) .

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because the Division did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application.

10. PEDIATRICS

The Applicant requested a full waiver of pediatric studies. The indication of treatment of atrophic vaginitis due to menopause does not occur in children. Rosemary Addy of the Pediatric Maternal Health Staff stated in her e-mail of May 15, 2008, that "the PeRC agreed with the waivers."

11. OTHER RELEVANT REGULATORY ISSUES

11.1 Division of Scientific Investigations

At the request of DRUP, 2 study sites for Study VAG-2195 were inspected by the Division of Scientific Investigation (DSI). According to the primary Clinical Reviewer, the DSI Clinical Inspection Summary, submitted to DRUP on June 5, 2008, indicated that there "*were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms*." A Form FDA 483, listing specific deficiencies, was issued to one of the sites (that of Dr. Koltrum). DSI concluded, however, that "*data generated for protocol VAG-2195 at this clinical site appear acceptable for use in support of NDA 20-908/013*."

11.2 Financial Disclosure Information

The primary Clinical Reviewer noted that financial disclosure information was submitted in the original application and appeared to be acceptable.

12. LABELING

The proposed proprietary name for 10 µg estradiol vaginal tablets is Vagifem, the same proprietary name as the currently marketed product (Vagifem 25 µg). The 2 products will be differentiated in labeling by prominent designation of the dose (10 µg or 25 µg). Comments regarding changes to the proposed carton labeling were received from the Division of Medication Error Prevention and Analysis (DMEPA) during the first review cycle and were incorporated by the Applicant. Carton labeling for both products will be identical, differing only by the dosage strength of the product. The Division of Risk Management (DRISK) reviewed proposed Patient Labeling during the first review cycle and suggested changes were incorporated as appropriate. The Package Insert for currently marketed Vagifem 25 µg was converted to Physician Labeling Rule (PLR) format and updated to include information for Vagifem 10 µg. Acceptable labeling, requiring only minor editorial revisions, was received from the Applicant on November 18, 2009. Final labeling was agreed-to on November 20, 2009.

Further details regarding labeling issues that were addressed during review of this Application are provided in Section 12 of the CDTL Review of the Applicant's Complete Response.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

Vagifem (estradiol vaginal tablets) 10 µg will be approved for the indication of *treatment of atrophic vaginitis due to menopause*. The dosing regimen is one tablet daily for 2 weeks, followed by one tablet twice weekly (for example, Tuesday and Friday).

13.2 Benefit/Risk Assessment

Treatment with Vagifem 10 µg was shown to be statistically superior to treatment with placebo tablets for each of the 3 protocol-specified co-primary efficacy endpoints. Treatment with Vagifem 10 µg was statistically superior to treatment with placebo in terms of: (1) reducing the severity of a composite score based on each subject's most bothersome symptom of atrophic vaginitis, (2) improving vaginal cytology (i.e., increasing the percentage of superficial cells and reducing the percentage of parabasal cells), and (3) reducing vaginal pH. The safety profile of Vagifem 10 µg was acceptable and was comparable to that for other approved estrogen vaginal products indicated for the treatment of atrophic vaginitis or the (b)(4).

Data provided in this Application indicate that Vagifem 10 µg, when used in accordance with to-be-approved labeling, will have a favorable benefit/risk profile and will be safe and effective for the treatment of atrophic vaginitis due to menopause.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing risk evaluation and mitigation strategies are warranted or requested.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

There are no recommendations for postmarketing requirements and commitments.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SCOTT E MONROE
11/25/2009

Summary Review for Regulatory Action

Date	October 14, 2008
From	Scott Monroe, MD
Subject	Division Director Summary Review
NDA	NDA 20-908/s-013
Applicant Name	Novo Nordisk, Inc
Date of Submission	December 7, 2007
PDUFA Goal Date	October 7, 2008 (Extended to January 7, 2008)
Proprietary Name / Established (USAN) Name	Vagifem® Estradiol vaginal tablet
Dosage Forms / Strength	Vaginal tablet / 10 µg
Proposed Indication(s)	(b)(4)
Proposed Regimen	One intravaginal tablet daily for 14 days followed by one intravaginal tablet twice weekly
Action	***Complete Response (see Section 13.1.1)***

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Theresa van der Vlugt, MD (primary reviewer)
Statistical Review	Shahla Farr, MS; Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Alexander Jordan, PhD; Lynnda Reid, PhD
CMC Review/ONDQA	Jean Salemme, PhD/Hasmukh Patel, PhD
Microbiology Review	Not needed
Clinical Pharmacology Review	Chongwoo Yu, PhD/Myong-Jin Kim, Pharm.D.
DDMAC	Not done
DSI	Jose Tavarez, MS/Constance Lewin, MD
CDTL Review	Shelley Slaughter, MD, PhD
OSE/DMEPA	Jinhee Lee, Pharm.D./Kellie Taylor, Pharm.D./Denise Toyer, Pharm.D.
OSE/DRISK	Nancy Carothers /Jodi Duckhorn, MA

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DSI	Division of Scientific Investigations
DRISK	Division of Risk Management
CDTL	Cross-Discipline Team Leader

DIVISION DIRECTOR SUMMARY REVIEW

1. INTRODUCTION

The objective of NDA 20-908/s-013 is to obtain marketing approval for a lower dosage strength of the currently approved and marketed drug Vagifem® (estradiol vaginal tablets) 25 µg. Vagifem (estradiol vaginal tablets) 25 µg was approved in 1999 for the indication of "atrophic vaginitis." In the present Application, Novo Nordisk seeks marketing approval for (estradiol vaginal tablets) 10 µg. The proposed dosing regimen for the new lower dosage product is identical to that of the presently marketed product: one intravaginal tablet daily for 14 days with twice weekly dosing thereafter. The proposed indication for the new lower dose product is "(b)(4) (b)(4)" The primary source of efficacy and safety data for the (estradiol vaginal tablets) 10 µg is Study VAG-2195, in which subjects were treated with study medication for up to 52 weeks. Study VAG-2195 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted in 308 healthy menopausal women, 45 years of age or older, at 45 sites in the U.S. and 4 sites in Canada.

1.1 Draft Guidance for Estrogen/Progestin Products

In 2003, the Agency issued a draft Guidance for Industry (hereafter referred to as the draft HT Guidance) entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation." The draft HT Guidance provides general information regarding the design and conduct of clinical trials for the treatment of the symptoms vulvar and vaginal atrophy (VVA). The information includes recommendations regarding (1) subject inclusion and exclusion criteria, (2) symptoms of VVA that could be suitable for study, and (3) the 3 co-primary endpoints that should be evaluated. The draft HT Guidance includes the following statement:

> "We recommend that studies be randomized, double blind, and of 12-week duration. In addition, we recommend that studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated."

The draft HT Guidance also states that for a successful outcome of a clinical trial for the treatment of the symptoms of VVA, treatment with the proposed drug product should demonstrate statistical superiority over treatment with placebo for <u>all</u> of the following 3 co-primary endpoints:

1. Mean change from baseline to Week 12 in the moderate to severe symptom of VVA that has been identified by the patient as being the most bothersome to her
2. Mean change from baseline in the vaginal maturation index at Week 12
   - Should show a statistically significant increase in vaginal superficial cells
   - Should show a statistically significant decrease in vaginal parabasal cells
3. Mean change from baseline in vaginal pH at Week 12
   - Should show a statistically significant lowering of vaginal pH

Division Director's Comments

- *The draft HT Guidance does not specifically address the issue of the analysis of the most bothersome symptom endpoint. More specifically, it is silent on the acceptability of a composite analysis, based on several symptoms, for this endpoint. For example, a composite endpoint analysis might be based on the overall change in severity of dyspareunia, vaginal dryness, and vaginal irritation. Alternatively, one could interpret the guidance as requiring that treatment with the proposed drug product demonstrate a statistically better effect than placebo for one or more individual symptoms of VVA (e.g., dyspareunia alone), without consideration of the effect of treatment on other symptoms of VVA.*
- *It was the intent of the principal author(s) of the Guidance that (1) treatment with the proposed drug product demonstrates a statistically better effect than placebo for one or more individual symptoms and (2) a composite analysis of improvement in VVA symptoms would not be an acceptable alternative. Because of this lack of clarity in the draft HT Guidance, Sponsors generally have been informed at their end-of-phase 2 meeting or as part of the Division's review of their Phase 3 protocol that the Division of Reproductive and Urologic Products (DRUP) does not recommend or support the use of a composite endpoint for the most bothersome symptom co-primary endpoint.*

1.2 Significant Review Issues

No safety issues, other than those expected with an estrogen product for the treatment of menopausal symptoms, were identified during the review of NDA 20-908/s-013. These safety issues would not preclude approval of an efficacious product for the (b)(4).

The only significant review issue concerned the outcome for the most important of the 3 co-primary efficacy endpoints (i.e., the change from baseline in the most bothersome symptom of VVA). Among the review issues related to this endpoint or outcome were:

- Was the Applicant clearly informed prior to initiation of the Phase 3 clinical trial that DRUP expected that the clinical trial be adequately powered to demonstrate a statistical improvement in one or more individual symptoms of VVA?
- Is a statistically significant improvement in a composite endpoint, based on several symptoms of VVA (e.g., dyspareunia, vaginal dryness, and vaginal irritation), adequate to support efficacy or must a successful clinical trial demonstrate a statistically significant improvement in at least one individual symptom of VVA?
- What is the appropriate statistical analysis for the efficacy data for the most bothersome symptom endpoint in Study VAG-2195? Did the distribution of the efficacy data necessitate the use of a nonparametric method?
- Was it necessary to make an adjustment for multiplicity because of the 3 different VVA symptoms (dyspareunia, vaginal dryness, and vaginal irritation) that were assessed for improvement in the analysis of the most bothersome symptom endpoint?

2. BACKGROUND

2.1 Products Available for the Treatment of VVA

Numerous estrogen (estradiol or conjugated estrogens) alone and estrogen plus progestin drug products are currently approved for the treatment of symptoms of VVA due to menopause. In general, the oral and transdermal products received approval and class labeling for a VVA indication as part of their approval for the treatment of vasomotor symptoms (VMS). In most instances, applicants for these oral and transdermal products were not specifically required to conduct an adequate and well controlled clinical trial specifically for the treatment of symptoms of VVA. Among the vaginal estrogen products approved for a VVA indication are Premarin® Vaginal Cream (conjugated estrogens cream), Estrace® Cream (estradiol cream), Vagifem® (estradiol vaginal tablets) 25 µg, Estring® (estradiol ring), and Femring® (estradiol ring).

2.2 Impact of WHI Findings on Labeling of Estrogen Products for the Treatment of VVA

The findings from the conjugated estrogen plus medroxyprogesterone acetate (MPA) substudy of the Women's Health Initiative (WHI), which were first reported in 2002 prompted significant revision of the class labeling for estrogen plus progesterone and estrogen alone products for the treatment of menopausal symptoms. Among these revisions were recommendations in labeling that:

- The use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.
- When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

2.3 Regulatory History

The protocol for VAG-2195 was first submitted in October 2004. The primary objective of the study was to assess the efficacy of (estradiol vaginal tablets) 10 µg, compared to placebo, for the treatment of symptoms of VVA. The secondary objective of Study VAG-2195 was to "evaluate the endometrial safety from endometrial biopsies taken at the beginning and at the end of study treatment (12 months)." In a letter dated February 1, 2005, DRUP provided Novo Nordisk with numerous comments and recommendations regarding Study VAG-2195 (the primary study in support of the efficacy of this NDA). Among the recommendations was the following statement (Item No. 8 in the letter):

*"**We do not recommend that a composite symptom score, as proposed, be calculated**."*

In February 2006, the Applicant amended the Protocol for Study VAG-2195. The Amendment included reducing the size of the trial from 600 subjects (400 in the [estradiol vaginal tablet] 10 µg arm and 200 in the placebo arm) to 300 subjects (200 in the [estradiol vaginal tablet] 10 µg arm and 100 in the placebo arm) because of slow enrollment.

Division Director's Comment

- *No clinical or statistical comments were provided to the Applicant regarding the reduction in the clinical trial population.*

On September, 2007, DRUP conveyed to Novo Nordisk a recommendation that the company request a pre-NDA meeting for the (estradiol vaginal tablet) 10 µg product. No request for such a meeting was made. In a letter dated November 15, 2007, DRUP provided Novo Nordisk with guidance regarding the primary efficacy analysis recommended by the Division for the indication of (b)(4) The guidance included the following:

- "The most bothersome symptom co-primary endpoint should be based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms."
- "We remind you of the information that was provided to you in our communication of February 1, 2005. This information included the following guidance in Item 8: "We do not recommend that a composite symptom score, as proposed, be calculated."
- "In accordance with our recommendation that a composite score not be used for the co-primary endpoint, your clinical trial should demonstrate that, compared to subjects treated with placebo, subjects treated with Vagifem 10 µg vaginal tablets have a statistically significant improvement in one or more of the individual symptoms listed in Item 1a above, as well as a statistically significant decrease in vaginal pH, and an increase in vaginal superficial cells, and a decrease in vaginal parabasal cells."

In addition, the November 15, 2007 letter requested that a final Statistical Analysis Plan (SAP) for Study VAG-2195 be submitted for review and comments prior to the submission of the supplemental NDA.

Division Director's Comment

- *The SAP was not submitted prior to submission of the NDA.*

NDA 20-908/s-013 was submitted on December 7, 2007. In the submission's cover letter, Novo Nordisk asserted in Item "1c" that the following had been addressed:

> *"**As recommended a composite symptom score was not calculated or used as a co-primary endpoint.**"*

Division Director's Comments

- *Based on my review of the communication between DRUP and the Applicant, I believe that the Applicant was adequately informed prior to initiation of Study VAG-2195 that DRUP did not support the use a composite endpoint for analyzing the improvement in subjects' most bothersome moderate to severe symptom of VVA.*
- *Had the Applicant submitted the SAP for Study VAG-2195 while the study was ongoing, DRUP would likely have noted that the planned analysis plan was based on, and powered for, a composite analysis rather than an analysis for demonstrating statistically significant improvement in one or more individual symptoms of VVA. In addition, the*

Applicant could have been advised at that time that an adjustment for multiplicity (which could have included a hierarchical analysis) would most likely be needed.

3. CMC/DEVICE

The primary Chemistry Reviewer, Jean Salemme, Ph.D., made the following statement in the Conclusions and Recommendations Section of her review:

> "*Adequate information has been provided to support this supplement. Additionally, the Office of Compliance recommends the proposed manufacturing site for approval. This supplement, therefore, is recommended for approval."*

The following information is also taken directly from Dr. Salemme's review:

> *"This efficacy supplement proposes an additional lower strength tablet, 0.010 mg estradiol, to be manufactured at a new drug product manufacturing site, Novo Nordisk in Maaloev, Denmark, with a scale-up in batch size from* (b)(4) *to* (b)(4) *with most of the approved chemistry, manufacturing and controls. The approved methods for identification, assay, related substances, and dissolution have been modified and validated for the analysis of both the 0.025 mg and the 0.010 mg tablets… The data show that the 0.010 mg batches meet the approved drug product specification and are comparable to the approved tablets.*"

Division Director Comment

- *I concur with the recommendations made by the primary Chemistry Reviewer. There are no outstanding CMC issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Estradiol is widely used in many products for the treatment of menopausal symptoms. In addition, the composition of (estradiol vaginal tablets) 10 µg is identical to that of presently marketed (estradiol vaginal tablets) 25 µg, with the exception of the quantity of estradiol (b)(4) (b)(4)). In the current NDA, Novo Nordisk referenced the non-clinical pharmacology/toxicology information contained in original NDA 20-908, Vagifem (estradiol vaginal tablets) 25 mcg. Therefore, according to the primary Pharmacology/Toxicology Reviewer, Alexander Jordan PhD, no new pharmacology, toxicology, or pharmacokinetic/toxicokinetic studies were necessary to support the current NDA submission (s-013). Dr. Jordan made the following comments and recommendations in his review:

> *"Based on the approval of Vagifem (estradiol vaginal tablet) 25 µg, which has the same formulation and dosing schedule as Vagifem 10 µg, Pharmacology considers Vagifem (estradiol vaginal tablets) 10 µg safe for the proposed indication.*"
>
> *Recommendations on approvability: "Pharmacology recommends approval of Vagifem (estradiol vaginal tablets) 10 µg."*
>
> *Recommendations for nonclinical studies: "None."*

Recommendations on labeling: "Labeling will be similar to Vagifem (estradiol vaginal tablets) 25 µg approved under NDA 21-840, which has the same formulation composition and dosing schedule and is used for the same indication."

Division Director Comment

- *I concur with the recommendation of Dr. Jordan that there are no outstanding nonclinical pharmacology/toxicology issues.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

In addition to the principal safety and efficacy study (VAG-2195), the Applicant also submitted the results of a bioavailability (BA) clinical trial (VAG-1850).

5.1 Study VAG-1850

Study VAG-1850 was a randomized, open label, multiple dose, parallel group, single center BA study conducted in 58 healthy post-menopausal women with atrophic vaginitis to evaluate the extent of systemic absorption of estradiol (E2) during treatment with (estradiol vaginal tablets) 10 µg and Vagifem® (estradiol vaginal tablets) 25 µg. Subjects received one of the 2 treatments. Subjects were treated once daily for the first 2 weeks and a twice weekly thereafter for the following 10 weeks. Table 1 and Table 2 summarize the plasma E2, estrone (E1), and estrone sulfate (E1S) AUC and $C_{ave(0\text{-}24\ hrs)}$ values uncorrected for baseline.

Table 1 Arithmetic Means for E2, E1, and E1S PK Parameters during Treatment with (Estradiol Vaginal Tablets) 10 µg (N=27)

	E2			E1			E1S		
	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both $AUC_{0\text{-}24}$ and $C_{ave(0\text{-}24)}$

Source: Table 1 of primary Clinical Pharmacology Review.

Table 2 Arithmetic Means for E2, E1, and E1S PK Parameters during Treatment with (Estradiol Vaginal Tablets) 25 µg (N=27)

	E2			E1			E1S		
	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]	$AUC_{0\text{-}24}$ (h.pg/ml)	$C_{ave(0\text{-}24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both $AUC_{0\text{-}24}$ and $C_{ave(0\text{-}24)}$

Source: Table 2 of primary Clinical Pharmacology Review.

Chongwoo Yu, PhD, the primary clinical Pharmacology Reviewer, made the following comment in the Executive Summary of his review regarding the pharmacokinetic findings:

> *"E2 administered into the vagina at repeated doses of 10 μg was found to display a PK profile that was globally similar in patterns to that following 25 μg administration. Mean plasma concentrations of E2, E1, and E1S were consistently lower for the Vagifem 10 μg tablet than the currently-marketed Vagifem (25 μg) formulation. The mean E2 plasma concentrations over 24 hr were always below 11 and 21 pg/ml for Vagifem 10 and 25 μg, respectively, even after 14 days of daily administration. Overall, mean E2 concentrations remained within the normal postmenopausal range in both groups, Vagifem 10 and 25 μg."*

5.2 Clinical Pharmacology Recommendation

Dr. Yu made the following recommendation in his review:

> *"The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 20-908 submitted on December 7, 2007 and April 18, 2008. The overall Clinical Pharmacology data submitted to support this NDA are acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language."*

No phase 4 commitments were recommended.

Division Director's Comment

- *I concur with Dr. Yu's recommendation that the Clinical Pharmacology data are sufficient to support approval of 10 μg estradiol vaginal tablets.*

6. CLINICAL MICROBIOLOGY

The primary Chemistry Reviewer, Dr. Salemme, determined that a microbiology consult for 10 μg estradiol vaginal tablets was not necessary. The proposed lower strength product will be subject to the same controls as the currently approved and marketed product.

Division Director Comment

- *I concur with this decision.*

7. CLINICAL/STATISTICAL-EFFICACY

7.1 Overview of Clinical Program

The primary source of efficacy data for (estradiol vaginal tablets) 10 μg was Study VAG-2195 in which subjects were treated with study medication for up to 52 weeks. Study VAG-2195 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial conducted in 308 healthy menopausal women, 45 years of age or older, conducted at 45 sites in the U.S. and 4 sites in Canada. Subjects were randomly assigned 2:1 to treatment with either (estradiol vaginal tablets) 10 μg or placebo vaginal tablets. The inclusion and exclusion criteria were consistent with those of other clinical trials for the treatment of symptoms of VVA.

7.1.1 Subject Demographics and Baseline Characteristics

The demographic and baseline characteristics for the randomized subjects in Study VAG-2195 are listed in Table 3. A total of 308 subjects took at least one dose of study medication (one subject in the placebo group did not start treatment). The mean age of the randomized subjects was 56.6 years and more than 90% of the subjects were white.

Table 3 Subject Demographics and Baseline Characteristics for Study VAG-2195

Characteristic	Placebo Vaginal Tablets n = 104	Estradiol Vaginal Tablets n = 205	Total n = 309
Mean Age (SD), years	57.7 (5.27)	57.5 (5.64)	57.6 (5.51)
Range	46 – 75	46 – 81	46 – 81
Race, n (%)			
White	95 (91.3)	192 (93.7)	287 (92.9)
Black or African American	4 (3.8)	6 (2.9)	10 (3.2)
Asian	3 (2.9)	2 (1.0)	5 (1.6)
American Indian or Alaskan Native	0	2 (1.0)	2 (0.6)
Native Hawaiian or Pacific Islander	0	1 (0.5)	1 (0.3)
Other	2 (1.9)	2 (1.0)	4 (1.3)
Body Weight, kg			
Mean (SD)	66.2 (12.0)	66.3 (10.5)	66.2 (11.0)
Range	45.8 – 99.6	40.8 – 95.3	40.8 – 99.6
Body Mass index, kg/m^2			
Mean (SD)	24.9 (4.3	25.2 (3.5)	25.1 (3.8)
Range	18.0 – 35.0	17.9 – 35.3	17.9 – 35.3
Time since last menses			
Mean (SD), yrs	8.2 (5.3)	8.0 (5.8)	8.1 (5.7)
Range	1 -29	1 – 32	1 – 32
< 2 yrs, n (%)	1 (1.0)	2 (1.0)	3 (1.0)
2 to < 5 yrs, n (%)	35 (33.7)	81 (39.5)	116 (37.5)
6 to < 10 yrs, n (%)	33 (31.7)	65 (31.7)	98 (31.7)
≥ 10 yrs, n (%)	35 (33.7)	57 (27.8)	92 (29.8)

Source: Table 2 of the FDA Statistical Review.

7.1.2 Disposition of Subjects

The disposition of subjects randomized in Study VAG-2195 is summarized in Table 4. Of the 309 randomized subjects, 34 subjects (32.7%) in the placebo treatment group and 41 subjects (20.0%) in the estradiol vaginal tablet treatment group discontinued before Week 52.

Table 4 Dispositions of Subjects in Study VAG-2195

	Placebo Vaginal Tablets n (%)	Estradiol Vaginal Tablets n (%)	Total n (%)
Number of subjects randomized	104	205	309
Number of subjects who completed	70 (67.3)	164 (80.0)	234 (75.7)
Number of subjects who discontinued	34 (32.7)	41 (20.0)	75 (24.3)
Reasons for discontinuation			
Adverse event	5 (4.8)	11 (5.4)	16 (5.2)
Protocol non-compliance	2 (1.9)	6 (2.9)	8 (2.6)
Ineffective therapy	11 (10.6)	6 (2.9)	17 (5.5)
Other	16 (15.4)	18 (8.8)	34 (11.0)

Source: Modified from Table 1 of the FDA Statistical Review.

Division Director Comments

- *The percentage of subjects who withdrawn because of adverse events was similar in the 2 treatment groups (4.8% in the placebo group and 5.2% in the estradiol group).*
- *The percentage of subjects who withdrawn because of lack of efficacy was higher in the placebo groups (10.6%) compared to that in the estradiol group (2.9%).*
- *The overall percentages of subjects who withdrew for specific reasons were relatively low for a one year clinical trial for the treatment of symptoms of VVA.*

7.2 Efficacy Findings

7.2.1 Primary Assessments and Endpoints

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause, the Agency's 2003 draft HT Guidance recommends the following 3 co-primary endpoints:

- Mean change from baseline to Week 12 in vaginal cytology (percentages of superficial and parabasal cells). For study inclusion, subjects should have no greater than 5% superficial cells on a vaginal smear at baseline. The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.
- Mean change from baseline to Week 12 in vaginal pH. For study inclusion, subjects should have a vaginal pH > 5.0 at baseline. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.
- Mean change from baseline to Week 12 in the moderate to severe self-assessed symptom of VVA identified by the subject as being the most bothersome to her. For study inclusion, subjects should self-identify the moderate to severe symptom of VVA that is most bothersome. The primary efficacy analysis should show a statistically significant improvement in the moderate to severe symptom identified as most

bothersome at baseline. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy in the draft HT Guidance include:

- Vaginal dryness (categorized as none, mild, moderate or severe)
- Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate, or severe)
- Dysuria (categorized as none, mild, moderate, or severe)
- Vaginal pain associated with sexual activity (categorized as none, mild, moderate, or severe)
- Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate, or severe)

Symptoms were assigned values of 0, 1, 2, or 3 for severities of none, mild, moderate, and severe, respectively, for the purpose of analyses.

The primary efficacy endpoints were assessed at Week 12 in accordance with the draft HT Guidance. For subjects who terminated before Week 12, the values for their last post-baseline assessment of vaginal cytology, vaginal pH, and severity of their most bothersome symptom of VVA was used in the respective analyses (a last observation carried forward or LOCF analysis).

7.2.2 Efficacy Findings for Vaginal Cytology and pH

Change in Vaginal Cytology

Table 5 shows the mean percentages of parabasal and superficial cells at baseline and Week 12 (or LOCF) and the changes from baseline. Data are limited to those subjects who at baseline met all 3 entry criteria, consisting of a pH of 5.0 or greater, superficial cells of no greater than 5%, and a most bothersome moderate to severe symptom of VVA.

Table 5 Baseline, Week 12, and Mean Change from Baseline in Vaginal Cytology in the Subset of Subjects Meeting Each of the Recommended Baseline Entry Criteria

	Observed Data			Change from Baseline
	Parabasal Cells (%)			
Visit **Treatment**	**N**	**Mean (SD)**		**Mean (SD)**
Baseline				
10 µg estradiol	149	47.8 (41.92)		
Placebo	77	49.8 (41.81)	-	-
Week 12 (LOCF)				
10 µg estradiol	146	5.7 (18.48)		-42.5 (45.84)
Placebo	77	39.7 (36.11)		-10.2 (44.33)
P-value				**<0.001**
	Superficial Cells (%)			
Visit **Treatment**	N	Mean (SD)		Mean (SD)
Baseline				
10 µg estradiol	149	0.5 (1.21)	-	-
Placebo	77	0.2 (0.61)		
Week 12 (LOCF)				
10 µg estradiol	148	15.3 (16.64)		14.7 (16.76)
Placebo	77	4.8 (8.05)		4.7 (8.04)
P-value	-	-	-	**<0.001**

Source: Modified from primary Medical Review for NDA 20-908/s-013, Table 12.

Division Director's Comment

- *Compared to placebo, there was a statistically significant greater reduction from baseline in the percentage of parabasal cells and a statistically significant greater increase from baseline in the percentage of superficial cells in the estradiol- treated subjects.*

Change in Vaginal pH

In Study VAG-2195, the Applicant assigned the measured vaginal pH values to one of 4 pH ranges (<5, 5-5.49, 5.5-6.49, and > 6.49). For the purpose of analyzing the changes in vaginal pH, the pH ranges were assigned numeric values, or scores, of 0, 1, 2, and 3, respectively, where a pH value of <5 = 0 and a pH value of >6.49 = 3. Using this convention, the mean pH scores at baseline and Week 12 (LOCF) and the mean change from baseline was calculated for each treatment group. Table 6 shows the mean baseline and Week 12 scores and the mean changes from baseline in the vaginal pH scores for those subjects who met all 3 entry criteria at baseline of a pH greater of 5.0 or greater, superficial cells of no greater than 5%, and a most bothersome moderate to severe symptom of VVA.

Table 6 Baseline, Week 12, and Mean Change from Baseline in Vaginal pH Score in the Subset of Subjects Meeting Each of the Recommended Baseline Entry Criteria

Visit Treatment	N	Vaginal pH score Mean (SD)		Change from Baseline in pH Score Mean (SD)
Baseline				
10 µg estradiol	149	2.3 (0.67)	-	-
Placebo	77	2.4 (0.64)		
Week 12 (LOCF)				
10 µg estradiol	147	1.0 (0.87)		-1.3 (1.02)
Placebo	77	2.0 (0.99)		-0.4 (0.77)
P-value				**<0.001**

Source: Modified from primary Medical Review for NDA 20-908/s-013, Table 15.

Division Director's Comments

- *Subjects treated with (estradiol vaginal tablets) 10 µg had a statistically greater reduction in vaginal pH from baseline at Week 12 (or LOCF) than subjects treated with placebo tablets.*
- *The estradiol group also showed a greater percentage of subjects with normalization of vaginal pH than the placebo group (71.8% vs. 36.3%, respectively), with normalization defined by the Applicant as a pH of < 5.5.*
- *I concur with the assessment of the primary Medical Reviewer that the use of a vaginal pH score, instead of actual pH values, is acceptable to assess the effect of treatment on vaginal pH. The primary Medical Reviewer further states in her review that "A pH score is consistent with labeling for the approved Vagifem® 25 mcg drug product."*

7.2.3 Most Bothersome Moderate to Severe Symptom of VVA

After submission of the NDA, there were numerous communications between DRUP and the Applicant in an effort to reach agreement and closure on the appropriate dataset and analysis for the most bothersome symptom endpoint. Among the issues that were addressed in these communications were:

1. The composition of the population of subjects that should form the basis of the analysis (i.e., DRUP and the Applicant initially differed in terms of the specific subjects in the different most bothersome VVA treatment groups for whom there were evaluable post-baseline efficacy data.
2. The appropriate analysis for the data from the respective populations (i.e., an ANCOVA or an ANCOVA on ranks because of the non-normal distribution of the data).
3. The need for an adjustment for multiplicity because Study VAG-2195 allowed for the assessed of improvement in more than one symptom of VVA.

Altogether, the Application submitted 4 major re-analyses for this endpoint after submission of the original NDA supplement. The last 2 of these re-analyses were submitted on October 2 and October 6, 2008, respectively. The primary Medical Reviewer has included the analyses

from each of these submissions (other than that of October 6) in her review. In this summary Review, I focus only on the final analyses, including that of October 6.

Division Director's Comment

- *Both the Applicant and DRUP initially did not include the full population of subjects with evaluable post-baseline efficacy data in their respective analyses. These errors were due to many factors, including (1) the Applicant not fully understanding the guidance that they had received from DRUP regarding which subjects to include and (2) the Applicant's classifying values for subjects who terminated prematurely in a non-obvious manner. At the end of the review process, however, DRUP and the Applicant had resolved their differences in terms of the composition of the dataset.*

Characteristics of the Population for the Analysis of the Change in Most Bothersome Symptom

The most bothersome symptom identified at baseline by the subjects enrolled in Study VAG-2195, the numbers of subjects who identified the symptom as most bothersome, and the distribution of the severity of each symptom are listed in Table 7. The symptoms of dyspareunia, vaginal dryness, and vaginal irritation accounted for virtually all of the symptoms. In the analyses of individual symptoms presented later in this Section, only these 3 symptoms are considered.

Table 7 Most Bothersome Baseline Symptom of VVA - Numbers of Subjects and Symptom Severity

Symptoms	Treatment Group	Severity of Symptom		
		Mild n	Moderate n	Severe n
Dyspareunia	Estradiol	5	37	63
	Placebo	4	20	37
Vaginal Dryness	Estradiol	5	41	12
	Placebo	2	24	1
Vaginal Irritation	Estradiol	2	15	8
	Placebo	3	6	1
Vaginal Soreness	Estradiol	0	3	2
	Placebo	0	0	0
Dysuria	Estradiol	2	0	1
	Placebo	0	0	0
Bleeding with Sexual Activity	Estradiol	1	1	1
	Placebo	0	0	0

Source: Modified from primary Medical Review for NDA 20-908/s-013, Table 16.

In the following discussion and analyses, the mITT-1 population refers to all subjects who reported a most bothersome moderate to severe symptom of VVA at baseline, took at least one dose of study drug, and had a post-baseline assessment of the symptom that had been identified as most bothersome. The mITT-2 population is a subset of the mITT-1 population

and includes only those subjects who also had a baseline vaginal pH of 5.0 or greater and a baseline vaginal cytology with ≤ 5.0 superficial cells.

Division Director's Comments

- *I believe that the primary efficacy analyses should be based on the mITT-1 population as it is closer to a true ITT population. It also is the Applicant's protocol-define population for the primary efficacy analysis.*
- *The primary clinical Review Team strongly prefers that the mITT-2 population be the basis for the primary efficacy analysis. I disagree with this position because I believe that the population of women who are most likely to use vaginal estrogen products for the treatment of VVA will be treated based on the severity of their symptoms, without regard to their vaginal pH or vaginal cytology. The clinical trial results obtained in the mITT-1 population are therefore more likely to reflect the effectiveness of the drug product in post approval clinical usage than the results obtained in the mITT-2 population.*

Composite Analysis - Change in Severity of Most Bothersome Moderate to Severe Symptom

In the Applicant's submission of October 2, 2008, a revision of the composite analysis included in the original NDA submission was provided. This revised analysis was based on the overall change in symptom severity scores across all symptoms in the mITT-2 population. In this composite analysis, shown in Table 8, the overall mean change from baseline in the severity of the subjects' most bothersome symptom was -1.3 and -0.9 in the (estradiol vaginal tablet) 10 µg- and placebo-treatment groups, respectively. The differences across treatments was statistically significant (P <0.001) according to the Applicant.

Table 8 Change in Severity of Most Bothersome Moderate to Severe Symptom – Composite Analysis (mITT-2 Population) and LOCF (Applicant's Analysis)*

Visit Treatment	Observed Data		Change from Baseline	Change in Severity: (Estradiol –Placebo) Mean (SD) p-value **
	N	Severity Mean (SD)	Severity Mean (SD)	
Baseline			-	
estradiol tablet	149	2.4 (0.50)	-	
Placebo tablet	77	2.4 (0.50)		
Week 12 (LOCF)				
estradiol tablet	141	1.1 (0.87)	-1.3 (0.88)	
Placebo tablet	74	1.5 (0.92)	-0.9 (0.88)	
				-0.43 (0.12)
				p <0.001

* mITT-2 population: All subjects with a most bothersome moderate to severe symptom of VVA and a vaginal pH ≥ 5.0 and ≤ 5% vaginal superficial cells.
** ANCOVA.
Source: Applicant's submission of October 2, 2008.

Division Director's Comments

- *Although a composite analysis provides useful information, DRUP recommended during the development stage for Protocol VAG-2195 that such an analysis not be the primary efficacy analysis.*
- *A composite analysis does not provide specific information for* (b)(4) *. As such, I consider this composite analysis to be supportive of efficacy and a secondary analysis. I do not consider a composite analysis as sufficient to be the primary efficacy analysis in support of approval for marketing for (estradiol vaginal tablets) 10 µg.*

Analyses of Individual Symptoms of VVA – mITT-2 Population

The FDA's analysis of the change in severity of the most bothersome moderate to severe symptoms of VVA, based on the mITT-2 population, is shown in Table 9. The FDA statistical team applied a test for normality to the data and determined that the data were not normally distributed; therefore a non-parametric analyses, an ANCOVA on ranks, was used to test for statistical significance. Among the 3 symptoms that had sufficient numbers of subjects for analysis, only the change in the severity of the dyspareunia score in the (estradiol vaginal tablet) 10 µg treatment group, relative to that in the placebo group, was associated with a p-value of < 0.05. However, because of multiplicity (i.e., 3 separate endpoints for the symptoms of dyspareunia, vaginal dryness, and vaginal irritation), an adjustment in the p-value was needed to determine if a treatment effect was statistically significant.

Table 9 Change in Severity of Most Bothersome Moderate to Severe Symptom of VVA – mITT-2 Population and LOCF (FDA Analysis) *

Symptom	Estradiol Vaginal Tablets		Placebo Vaginal Tablets		p-value **
	N	Mean Score	N	Mean Score	
Baseline					
Dyspareunia	76	2.62	46	2.63	
Vaginal Dryness	36	2.14	22	2.05	
Vaginal Irritation	21	2.32	6	2.17	
Week 12 (LOCF)		**Change from baseline**		**Change from baseline**	
Dyspareunia	76	-1.26	46	-0.89	0.020
Vaginal Dryness	36	-1.40	22	-0.91	0.093
Vaginal Irritation	21	-1.33	6	-1.00	0.714

* mITT-2 population: All subjects with a most bothersome moderate to severe symptom of VVA and a vaginal pH ≥ 5.0 and ≤ 5% vaginal superficial cells.
** ANCOVA based on ranks.
Source: Modified from FDA Statistical Review, Tables 3 and 4.

Division Director's Comment

- *Using a Bonferroni adjustment for the data represented in this analysis, a p-value of < 0.0167 (i.e., 0.05/3 = 0.0167) would be needed to declare a statistically significant change from baseline, beyond that of placebo treatment, for one or more of the 3 VVA*

symptoms in the (estradiol vaginal tablet) 10 µg treated subjects. The p-value for the change in dyspareunia was 0.02, and therefore, the difference in the effect of treatment with 10 µg estradiol vaginal tablets, compared to that of treatment with placebo, was not statistically significant.

- *It appears that the study is underpowered for the magnitude of the treatment effect. It is possible that treatment with (estradiol vaginal tablets) 10 µg would have been statistically superior to treatment with placebo for both reduction in dyspareunia and reduction in vaginal dryness if the Applicant had not reduced the size of the study by 50%. This is particularly unfortunate because of the Division's efforts to have Applicant's identify the lowest effective dose for estrogen products for the treatment of menopausal symptoms.*

The Applicant provided their independent analyses, limited to the symptom of dyspareunia, using the same dataset as that used by the FDA. The Applicant reported that the p-values for their analyses were p = 0.015 (based on an ANCOVA) and p = 0.017 (based on an ANCOVA on ranks, non parametric analysis) (see Table 10).

Table 10 Change in Severity of Dyspareunia: mITT-2 Population and LOCF (Applicant's Analysis)*

Visit Treatment	Observed Data N	Observed Data Severity Mean (SD)	Change from Baseline Severity Mean (SD)	Change in Severity: (Estradiol –Placebo) Mean (SD) p-value
Baseline			-	
estradiol tablet	84	2.6 (0.49)	-	
Placebo tablet	49	2.6 (0.49)		
Week 12 (LOCF)				
estradiol tablet	76	1.4 (0.99)	-1.3 (0.91)	
Placebo tablet	46	1.8 (0.92)	-0.8 (0.92)	
				-0.42 (0.17) **p = 0.015 **** **p = 0.017 *****

* mITT-2 population: All subjects with a most bothersome moderate to severe symptom of VVA and a vaginal pH ≥ 5.0 and ≤ 5% vaginal superficial cells.
** ANCOVA based on original score.
*** ANCOVA based on ranks (non-parametric analysis).
Source: Applicant's submission of October 2, 2008.

Division Director's Comments

- *The FDA statistical Team Leader, Dr. Sobhan, discussed with the Applicant's statistician the procedure that the Applicant had used for the ANCOVA on ranks analysis. Based on this discussion, Dr. Sobhan concluded that the specific ANCOVA on ranks procedure used by the Applicant's statistical team was not appropriate and that the p-value obtained by the FDA statistical analysis (p = 0.02) was the correct value. The FDA statistical review team does not accept the Applicant's p-value of 0.017 as valid.*
- *The Applicant argued in their submission of August 20, 2008, that an adjustment for multiplicity was not warranted because they had never intended to analyze the endpoint for the most bothersome symptom in terms of individual symptoms. This statement is*

inconsistent with the recommendation that was provided to the Applicant in DRUP's letter of February 1, 2005. It also is inconsistent with the Applicant's NDA cover letter in which it is stated: "As recommended, a composite symptom score was not calculated or used as a co-primary endpoint."

- *The Applicant further argued in the submission of August 20, 2008, that if an adjustment for multiplicity were warranted, a hierarchical testing procedure, based on the rank order of symptoms (in which dyspareunia would be the first symptom to be tested), would be appropriate. Had this hierarchical approach been declared in the protocol or SAP prior to unblinding, it would have been acceptable. Proposing the use of a hierarchical analysis post hoc, after the outcome is known, is not acceptable.*

Analyses of Individual Symptoms of VVA – mITT-1 Population

The primary Medical Reviewer and the medical Team Leader believe that the primary efficacy analysis for the change in severity of the most bothersome symptom should be based on the mITT-2 population. As presented earlier in this review, I believe that the primary efficacy analysis for the most bothersome symptom should be based on the mITT-1 population. The FDA's analysis of the change in severity of the most bothersome moderate to severe symptom of VVA, based on the mITT-1 population is shown in Table 11. For this data set, the FDA statistical team also tested the distribution of the data for normality and determined that the data were not normally distributed; therefore an ANCOVA on ranks was used to test for statistical significance.

Table 11 Change in Severity of Most Bothersome Moderate to Severe Symptom of VVA – mITT-1 Population and LOCF (FDA Analysis) *

Symptom	Estradiol Vaginal Tablets		Placebo Vaginal Tablets		p-value **
	N	Mean Score	N	Mean Score	
Baseline					
Dyspareunia	89	2.64	52	2.65	
Vaginal Dryness	52	2.23	25	2.04	
Vaginal Irritation	22	2.36	7	2.14	
Week 12 (LOCF)		**Change from baseline**		**Change from baseline**	
Dyspareunia	89	-1.21	52	-0.96	0.116
Vaginal Dryness	52	-1.35	25	-0.92	0.221
Vaginal Irritation	22	-1.32	7	-1.14	0.835

* m ITT-1 includes all subjects with most bothersome symptom of moderate to severe dyspareunia at baseline without regard to vaginal pH or cytology.
** ANCOVA based on ranks.
Source: Modified from FDA Statistical Review, Tables 5 and 6.

Division Director's Comment

- *None of decreases from baseline in the (estradiol vaginal tablet) 10 µg treatment group for the 3 symptoms of VVA that were studied were statistical greater than the respective decreases in the placebo treatment group. The p-values for the differences based on an*

ANCOVA on ranks ranged from 0.116 (dyspareunia) to 0.835 (vaginal irritation). Because none of these p-values were <0.05, further adjustment for multiplicity was not performed.

The Applicant was asked to provide an independent analysis of the same dataset (mITT-1 population) for the symptom of dyspareunia. The Applicant reported that the p-values for their analyses were p = 0.066 (ANCOVA) and p = 0.079 (ANCOVA on ranks, non parametric analysis) (see Table 12).

Table 12 Change in Severity of Dyspareunia – mITT-1 Population (Applicant's Analysis) *

Treatment	Baseline		Week 12 (LOCF)		Change from Baseline (P-value)
	N	Severity Mean (SD)	N	Severity Mean (SD)	Severity Mean (SD)
Estradiol	100	2.6 (0.49)	91	1.4 (0.95)	-1.2 (0.89)
Placebo	57	2.6 (0.48)	52	1.7 (0.99)	-0.9 (0.95)
					(p=0.066) *
					(p=0.079) **

* m ITT-1 includes all subjects with most bothersome symptom of moderate to severe dyspareunia at baseline without regard to vaginal pH or cytology.
** ANCOVA based on original score.
*** ANCOVA based on rank (non parametric).
Source: Applicant's submission of October 6, 2008, pg 5 and 6.

Division Director's Comments

- *Treatment with (estradiol vaginal tablets) 10 µg was not statistically superior to treatment with placebo, based on either the FDA or the Applicant's statistical analysis of the mITT-1 population, in reducing the severity of an individual most bothersome symptom.*
- *Because I believe that the mITT-1 population is the appropriate population for the primary efficacy analysis, I have considered the lack of efficacy using the analysis based on this population to be particularly compelling in my assessment of the approvability of (estradiol vaginal tablets) 10 µg (see Section 13.1.1).*

7.2.4 Assessment of Efficacy (FDA Statistical Review)

The FDA statistical reviewers (Ms. Farr and Dr. Sobhan) made the following statement in the Conclusions and Recommendations section of their review of NDA 20-908/s-013:

> *"Based on the data from a single study (VAG-2195), the results do not support the efficacy of Vagifem in reducing the severity of* (b)(4) *Although Vagifem did demonstrate superiority in vaginal pH and maturation index, but it failed to demonstrate statistically significant reductions in the severity of most bothersome symptoms compared to placebo. Based on our analysis using non-parametric method, which is the appropriate analysis method for the submitted data, we do not agree with the sponsor's claim, that vagifem is superior to placebo in* (b)(4) (b)(4) *after adjustment for multiplicity. The results in subjects meeting criteria of moderate to severe most bothersome symptom at baseline only, without regard to*

PH and superficial cells, also demonstrate that Vagifem 10 μg was not statistically significantly superior to placebo in the improvement of vaginal atrophy symptoms.

Therefore, from a statistical perspective, treatment with Vagifem 10 μg did not demonstrate statistically significant improvement in each of the three most bothersome symptoms compared to placebo."

7.3 Overall Assessment of Efficacy

In Study VAG-2195, treatment with (estradiol vaginal tablets) 10 μg was shown to be superior to treatment with placebo tablets for 2 of the 3 co-primary efficacy endpoints. Treatment with (estradiol vaginal tablets) 10 μg was statistically superior to treatment with placebo in terms of (1) reducing vaginal pH and (2) improving vaginal cytology (i.e., increasing the percentage of superficial cells and reducing the percentage of parabasal cells). Treatment with (estradiol vaginal tablets) 10 μg, however, was not shown to be superior to treatment with placebo in terms of reducing the severity of any individual moderate to severe symptom of VVA identified by subjects at baseline as being most bothersome to them.

Division Director's Comment

- *Of the 3 co-primary endpoints for the treatment of symptoms of VVA, improvement in a subject's most bothersome symptom of VVA is of greatest importance. Based on the data submitted for the protocol-defined modified ITT population (mITT-1), treatment (estradiol vaginal tablets) 10 μg did not result in a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual moderate to severe most bothersome symptom of VVA. The mITT-1 population consisted of all subjects with a moderate to severe most bothersome symptom of VVA at baseline, without regard to their baseline vaginal pH or vaginal cytology. In the analysis of the mITT-2 population (representing only those subjects who identified at baseline a most bothersome moderate to severe symptom and who had a vaginal pH of ≥ 5.0 and a vaginal cytology with ≤ 5% superficial cells), subjects treated with (estradiol vaginal tablets) 10 μg also did not demonstrate a statistically significant greater reduction in the severity of at least one individual moderate to severe symptom of VVA, when the analysis was appropriately adjusted for multiplicity.*

8. SAFETY

The primary Medical Reviewer has provided a thorough discussion and review of the safety findings for (estradiol vaginal tablets) 10 μg in her primary review, based on (1) the data provided in the origin submission of NDA 20-908/s-013, (2) the 4-month safety update, and (3) a review by Adrienne Rothstein, Pharm.D. (Office of Surveillance and Epidemiology) of postmarketing safety data in the FDA's Adverse Event Reporting System (AERS) database. The medical Team Leader also has reviewed the safety data provided in the current submission. Neither of these Medical Officers identified any safety issues that would suggest that the overall safety profile for (estradiol vaginal tablets) 10 μg would be less acceptable than that for other currently approved vaginal estrogen products. My comments regarding the safety of (estradiol vaginal tablets) 10 μg is based on the findings from Study VAG-2195 unless otherwise indicated.

8.1 Safety Population

The primary source of safety data for (estradiol vaginal tablets) 10 µg was Study VAG-2195, in which subjects were treated with study medication for up to 52 weeks. Study VAG-2195 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial conducted in 308 healthy postmenopausal women, 45 years of age or older, at 45 sites in the U.S. and 4 sites in Canada. Subjects were randomly assigned 2:1 to treatment with either (estradiol vaginal tablets) 10 µg or placebo vaginal tablets. The inclusion and exclusion criteria were consistent with those of other clinical trials for the treatment of VVA. One major safety objective of Study VAG-2195 was the evaluation of endometrial safety as assessed by endometrial biopsy at the end of treatment. Other safety assessments included vital signs, physical examination, gynecological examination, papanicolaou cervical smear, transvaginal ultrasound, and monitoring of adverse events.

Division Director's Comment

- *Although the overall safety database is not large, it is adequate for a low dose estrogen vaginal product for the treatment of VVA. The composition of (estradiol vaginal tablets) 10 µg differs from that of the approved and marketed 25µg drug product only in that the dose of estradiol hemihydrate has been reduced from 25.8 µg to 10.3 µg* (b)(4) (b)(4) *Based on the finding from PK Study VAG-1850, the systemic exposure to estradiol is lower during treatment with (estradiol vaginal tablets) 10 µg than that during treatment with the presently marketed 25 µg drug product.*

8.2 Deaths and Other Serious Adverse Events

There were no deaths in Study VAG-2195 or in the supportive PK study (Study VAG-1850). In Study VAG-2195, 7 of 208 subjects reported serious adverse events. (5/205 [2.4%] subjects in the estradiol treatment group and 2/103 [2%] subjects in the placebo group). The 5 serious adverse events in the estradiol treatment group were one case each of ventricular extrasystoles (premature ventricular contractions), acute cholecystitis, pneumonia, infra-orbital squamous cell carcinoma, and endometrial cancer. The 2 serious adverse events in the placebo treatment group were one case each of coronary artery stent occlusion and gastrointestinal hemorrhage.

In the Applicant's 4-month safety update, a single death was reported in the open-label non-IND Study VAG-1748. The single death (a 77-year old women receiving [estradiol vaginal tablets] 10 µg) was attributed to cerebral metastasis of a primary unknown cancer and was assessed as "unlikely related" to study medication by the investigator and the Applicant.

Division Director Comments

- *Overall, the percentage of subjects reporting serious adverse events in 52-week Study VAG-2195 was low and was similar in the estradiol and placebo treatment groups.*
- *The percentage of subjects reporting serious adverse events and the specific events do not raise any concerns about the overall safety of (estradiol vaginal tablets) 10 µg.*
- *The single case of endometrial adenocarcinoma in the estradiol treatment group in Study VAG-2195 is discussed in Section 8.3 (Division Director's Comments).*

8.3 Discontinuations for Adverse Events

Of the 308 subjects who received study drug, 74 subjects discontinued prematurely (41/205 [20.0%] in the estradiol treatment group and 33/103 [32.0%] in the placebo group) (see Table 4). Fifteen (15) of the 308 subjects discontinued prematurely because of an adverse event (11/205 [5.4%] in the estradiol treatment group and 4/103 [3.9%] in the placebo group). The specific adverse events that were associated with premature terminations (listed by treatment group) and day of onset/diagnosis are presented in Table 13.

Table 13 Adverse Events Associated with Premature Terminations

Subject ID	Day of Onset/Diagnosis	Adverse Event
Estradiol Vaginal Tablets		
(b)(6)	3	Vaginal hemorrhage, uterine spasm
	3	Abdominal pain, back pain, vaginal discharge
	4	Abdominal pain, back pain, pelvic discomfort
	4	Rash
	32	Anorexia, nausea, hot flush, depression
	45	Vaginal discharge, vulvovaginal pruritus
	111	Breast tenderness
	135	Cystitis
	271	Hepatic enzyme increased
	326	Endometrial cancer, Stage 2
	(not provided)	Pneumonia
Placebo Vaginal Tablets		
(b)(6)	2	Vaginal discharge, abdominal distention, peripheral edema, headache, back pain
	7	Hypertension, hypoesthesia
	20	Nausea, peripheral edema
	26	Stent occlusion

Source: Modified from Primary Medical Review, Section 7.1.3.

Division Director's Comments

- *As shown above, the reported adverse events resulting in discontinuation in Study VAG-2195, with the exception of endometrial cancer, are commonly associated with estrogen therapy for menopausal symptoms.*
- *Treatment with estrogen alone is well known to produce endometrial hyperplasia and less frequently endometrial cancer. Because of this risk, class labeling for estrogen products recommends the use of a progestin (continuous or intermittent). In Study VAG-2195, subjects were treated with estradiol alone because the assessment of endometrial safety in the absence of a concomitant or intermittent progestin was a secondary objective.*
- *Overall, the percentage of subjects who discontinued prematurely was low for a 52-week study for the treatment of VVA; the overall findings do not raise any new safety concerns.*

8.4 Common Adverse Events

Adverse events reported in at least 5% of subjects in either treatment group in Study VAG-2195 are listed in Table 14.

Table 14 Common Adverse Events (Reported in ≥ 5% of Subjects) in Study VAG-2195

Adverse Event	Estradiol Vaginal Tablet (N=205) n (%)	Placebo Vaginal Tablet (N=103) n (%)
Vulvovaginal mycotic infection	17 (8.3)	3 (2.9)
Vulvovaginal pruritus	16 (7.8)	2 (1.9)
Headache	15 (7.3)	13 (12.6)
Nasopharyngitis	14 (6.8)	7 (6.8)
Back pain	14 (6.8)	2 (1.9)
Vaginal discharge	12 (5.9)	8 (7.8)
Diarrhea	11 (5.4)	0 (0.0)

Source: Modified from Table 27, Primary Medical Review, Section 7.1.5.3.

Division Director's Comments

- *The most commonly reported treatment-emergent adverse events in Study VAG-2195 and Study VAG-1850 (not listed in this Memorandum) do not raise any new safety issues for an estradiol vaginal product.*

8.5 Endometrial Safety Findings

8.5.1 Endometrial Thickness

All subjects in Study VAG-2195 had a transvaginal ultrasound (TVU) performed prior to an endometrial biopsy at screening and at Week 52 (or sooner if clinically indicated or at early termination). Per the study protocol, subjects whose double-wall endometrial thickness measured by TVU was > 4 mm at screening were not eligible for enrollment. Mean endometrial thickness at baseline was 2.20 mm and 2.31 in the placebo-treated and estradiol-treated groups, respectively. Mean endometrial thickness at the end-of treatment was 2.21 and 2.47 mm in the placebo-treated and estradiol-treated groups, respectively.

8.5.2 Endometrial Biopsy Findings

All subjects in Study VAG-2195 had an endometrial biopsy performed at screening and at the end-of-study or early termination, provided the subject had been treated for 3 months or longer. Among 79 posttreatment biopsies in the placebo treatment group, there were no abnormal findings. Among the 172 posttreatment biopsies in the estradiol treatment group, there was a single case of complex hyperplasia without atypia and a single case of adenocarcinoma.

Division Director's Comments

- *Although PK Study VAG-1850 indicated that treatment with 10 µg estradiol vaginal tablets produced only a small increase in mean plasma estradiol concentrations, there was a small numeric increase in mean endometrial thickness in the estradiol-treated subjects.*
- *A total of 25 subjects in Study VAG-2195 had a TVU double-wall endometrial thickness ≥ 4 mm at Week 52 or at early termination. Of these 25 subjects, 21 were in the estradiol treatment group.*

- *The single case of complex hyperplasia without atypia was not likely secondary to treatment with study drug because the subject was treated for only 9 days. The single case of adenocarcinoma of the endometrium diagnosed after approximately one year of treatment may have been related to estradiol treatment. Treatment with estrogen alone is well known to produce endometrial hyperplasia and less frequently endometrial cancer. Because of this risk, class labeling for estrogen products recommends the use of a progestin (continuous or intermittent) in women with a uterus treated with an estrogen product. I agree with the recommendations of the primary Medical Reviewer and the medical Team Leader than labeling for (estradiol vaginal tablets) 10 µg should include the class recommendation regarding the use of a progestin should this drug product be approved at a later date.*

8.6 Overall Assessment of Safety

The primary Medical Reviewer made the following summary statements regarding the safety of (estradiol vaginal tablets) 10 µg in Section 1.3.3 of her review:

> *"The safety data presented in the submission demonstrates an acceptable overall safety profile of the 10 µg estradiol vaginal tablet, administered intravaginally daily for two weeks and then twice-weekly thereafter…The SAEs reported in Study VAG-2195 do not raise safety concerns."*

The medical Team Leader made the following summary assessment regarding the safety of (estradiol vaginal tablets) 10 µg on page 15 of her review:

> *"Overall, the safety profile as presented in the integrated summary of safety is acceptable and is not sufficiently different from previously approved estrogen-only products (including the 25 mcg dose of Vagifem®) to raise any additional concerns or to not receive class labeling."*

Division Director Comments

- *I concur with the overall assessments of the primary Medical Reviewer and the medical Team Leader that the safety profile of (estradiol vaginal tablets) 10 µg raises no new concerns and is acceptable for an estrogen vaginal product.*
- *The safety profile for (estradiol vaginal tablets) 10 µg in general clinical use would likely be comparable to that of other vaginal estrogen drug products approved* (b)(4) (b)(4)

9. ADVISORY COMMITTEE MEETING

This Application was not presented to an Advisory Committee (AC) because the Division did not believe that AC guidance was needed to make a regulatory decision concerning the approvability of the Application.

10. PEDIATRICS

The Applicant requested a full waiver of pediatric studies. The indication (b)(4) (b)(4) does not occur in children. Rosemary Addy of the Pediatric Maternal Health Staff stated in her e-mail of May 15, 2008, that "the PeRC agreed with the waivers."

11. OTHER RELEVANT REGULATORY ISSUES

11.1 Division of Scientific Investigations

At the request of DRUP, 2 study sites were inspected by the Division of Scientific Investigation (DSI). According to the primary Medical Reviewer, the DSI Clinical Inspection Summary, submitted to DRUP on June 5, 2008, indicated that there "were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms." A Form FDA 483, listing specific deficiencies, was issued to one of the sites (that of Dr. Koltrum). DSI concluded, however, that "data generated for protocol VAG-2195 at this clinical site appear acceptable for use in support of NDA 20-908/013."

11.2 Financial Disclosure Information

The primary Medical Reviewer noted that financial disclosure information was submitted and appeared to be acceptable.

12. LABELING

Labeling was not discussed with the Applicant during this review cycle. If the Applicant provides adequate evidence to support the efficacy of (estradiol vaginal tablets) 10 µg for the (b)(4) (b)(4)

Medication Errors Prevention and Analysis and the Division of Risk Management. These will be addressed during the next review cycle.

13. DECISION/ACTION/RISK BENEFIT ASSESSMENT

13.1 Regulatory Action

13.1.1 Decision of Division Director

This Application will not be approved during this review cycle. Adequate evidence was not provided in NDA 20908/s-013 to support the effectiveness of (estradiol vaginal tablets) 10 µg (b)(4) Based on the data submitted for the protocol-defined modified ITT population (mITT-1), subjects treated with (estradiol vaginal tablets) 10 µg did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual moderate to severe most bothersome symptom of VVA. The mITT-1 population consisted of all subjects with a moderate to severe most bothersome symptom of VVA at baseline, without regard to their baseline vaginal pH or vaginal cytology. In the analysis of the mITT-2 population (representing only those subjects who identified at baseline a most bothersome moderate to severe symptom and who had a vaginal pH of ≥ 5.0 and a vaginal cytology with $\leq 5\%$ superficial cells), subjects treated with (estradiol vaginal tablets) 10 µg also did not demonstrate a statistically significant greater reduction in the severity of at least one individual moderate to severe symptom of VVA, when the analysis was appropriately adjusted for multiplicity. This decision to not approve (estradiol vaginal tablets) 10 µg is

consistent with the recommendations of both the primary Medical Reviewer and the medical Team Leader (see Section 13.1.2).

13.1.2 Recommendations of Primary Medical Reviewer and Cross-Discipline Team Leader (Medical Team Leader) regarding Approvability

The primary Medical Reviewer, Dr. van der Vlugt, made the following recommendation in the Executive Summary of her review:

> *"The reviewer does not recommend approval of the 10 µg estradiol vaginal tablet for the "treatment of* (b)(4) (b)(4) *" Sufficient evidence was not provided in the application to conclude that the 10 µg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions was efficacious in the* (b)(4) *when compared to placebo. The safety of the 10 µg estradiol vaginal tablet was not a major concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved* (b)(4)

The medical Team Leader, Dr. Slaughter, made the following recommendation in the Introduction Section of her review regarding approvability:

> *"Should not be approved. The data included in supplement failed to demonstrate efficacy for estradiol vaginal tablet for the* (b)(4) (b)(4) *."*

On page 13 of her review, the medical Team Leader also made the following statement:

> *"The 2003 Draft HT Clinical Trial Guidance, recommends that to be considered efficacious, estrogen or estrogen/progestin drug products when compared to placebo, should demonstrate statistically significant improvement in the subject's self-identified most bothersome moderate to severe symptom (reduction in severity), vaginal superficial (increase in percentage) and parabasal (reduction in percentage) cells and vaginal pH (reduction). The data presented in this efficacy supplement met the vaginal superficial cells, vaginal parabasal cells and vaginal pH co-primary criteria for efficacy, but not the most important criteria for* (b)(4) (b)(4)

13.1.3 Resolution of Clinical and Statistical Deficiencies

To address the deficiency of this submission, the Applicant will need to conduct and submit the results of an adequate and placebo-controlled trial that demonstrates the efficacy of (estradiol vaginal tablets) 10 µg for the (b)(4) (b)(4). In accordance with the draft HT Guidance, the trial should enroll subjects with a self-identified most bothersome moderate-to-severe symptom of VVA due to menopause, vaginal pH of greater than 5.0, and 5% or fewer superficial cells on a smear from the vaginal wall. The trial should be powered to demonstrate at Week 12 the following: (1) a statistically significant improvement over placebo for at least one individual symptom of VVA self-identified by subjects as most bothersome at baseline; (2) a decrease in vaginal pH; and (3) an increase in superficial cells and a decrease in parabasal cells on a smear from the

vaginal wall. If the Applicant does not pre-specify a single individual most bothersome symptom that will be investigated, the statistical analysis plan will need to address the issue of multiplicity.

13.2 Benefit/Risk Assessment

13.2.1 Efficacy Considerations

Adequate evidence was not provided in NDA 20908/s-013 to support the effectiveness of (estradiol vaginal tablets) 10 µg (b)(4) (b)(4). Based on the data submitted for the protocol-defined modified ITT population (mITT-1), subjects treated with (estradiol vaginal tablets) 10 µg did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual moderate to severe most bothersome symptom of VVA. In the analysis of the mITT-2 population, treatment with (estradiol vaginal tablets) 10 µg also did not demonstrate a statistically significant greater reduction in the severity of at least one individual moderate to severe symptom of VVA when appropriately adjusted for multiplicity.

13.2.2 Safety Considerations

The safety profile of (estradiol vaginal tablets) 10 µg, based on the data provided in this submission, is acceptable for an estrogen drug product for the (b)(4) (b)(4)Postmarketing safety data from Vagifem (estradiol vaginal tablets) 25 µg, which has been marketed in the U.S. since 2000, do not raise any unique safety concerns.

13.2.3 Overall Risk/Benefit Assessment

Treatment with (estradiol vaginal tablets) 10 µg was not shown to be statistically superior to treatment with placebo in terms of a reduction in the severity of at least one individual most bothersome moderate to severe symptom of VVA; consequently, the risk/benefit profile does not support approval of the drug product for the proposed indication.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are warranted or requested.

13.4 Recommendation for Other Postmarketing Study Commitments

There are no recommendations for postmarketing study commitments

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/s/

Scott Monroe
10/14/2008 08:07:52 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

CROSS DISCIPLINE TEAM LEADER REVIEW(S)

Cross-Discipline Team Leader Review

Date:	November 20, 2009
From:	Shelley R. Slaughter, M.D., Ph.D.
NDA:	20-908/SE2-013/CR
Applicant:	Novo Nordisk, Inc,
Date of Submission:	May 26, 2009
PDUFA:	November 26, 2009
Requested Proprietary Name/ Established (USAN) name:	Vagifem® estradiol vaginal tablet
Dosage forms/Strength:	10 mcg estradiol vaginal tablet
Regimen:	one tablet inserted intravaginally daily for two weeks followed by one tablet inserted intravaginally twice weekly continuously
Proposed Indication:	(b)(4) (source: Form 356h)
Recommendation:	I am in alignment with the recommendation that this lower 10 mcg dose of Vagifem® be approved for the treatment of atrophic vaginitis due to menopause, the same indication as the currently approved 25 mcg dose of Vagifem®. I do not recommend granting an indication for (b)(4)

Executive Summary:

1. Introduction

With this complete response, Novo Nordisk is seeking an indication of (b)(4) (b)(4) for a lower dose (10 mcg) of its approved product Vagifem (25 mcg estradiol vaginal tablet). Supplemental NDA 20-908/SE1-013 was submitted on December 7, 2007. The supplemental application was supported by a single placebo-controlled, Phase 3 efficacy and safety study and a Phase 1 pharmacokinetic and safety study.

The overriding review issue for the original lower dose efficacy supplement 13 (and for the consideration of this complete response) was the efficacy of the 10 mcg drug product. Safety of this lower dose version of the approved product Vagifem® was not an issue. The 2003 Draft Guidance for Industry entitled, "ESTROGEN AND ESTROGEN/PROGESTIN DRUGS PRODUCTS TO TREAT VASOMOTOR SYMPTOMS AND VULVAR AND VAGINAL ATROPHY SYMPTOMS – RECOMMENDATIONS FOR CLINICAL EVALUATION" (henceforth referred to in this review as the 2003 Draft HT Clinical Trial Guidance) recommends that for a non-new molecular entity (b)(4) (b)(4) a single clinical trial be conducted that demonstrates for the drug product vs. placebo statistically significant improvement in the co-primary endpoints of: mean change (i.e. reduction in severity) in **the** (*intended as individual*) moderate to severe most bothersome symptom; mean change (increase)in vaginal superficial and vaginal parabasal cells (decrease) obtained from a smear of the lateral vaginal wall and mean change (reduction) in the vaginal pH. The 2003 Draft HT Clinical Trial Guidance further recommends that the population to be randomized to trials for symptoms of vulvar and vaginal atrophy, be composed of women who at baseline meet the criteria of at least one moderate to severe symptom of vulvar and vaginal atrophy that the woman (not the physician) has identified as most bothersome to her, a vaginal pH greater or equal to 5 and less than 5% superficial vaginal cells on the smear.

In the original supplement review cycle, analyses of symptom severity between baseline and week 12 for the 10 mcg estradiol vaginal tablet versus placebo demonstrated an unadjusted p-value of 0.020 (non-parametric analysis) for the moderate to severe most bothersome symptom of dyspareunia. When adjusted for multiplicity, this did not reach statistical significance (Bonferroni statistical significance assessed at 0.016 after adjustment for the selection from 3 symptoms). Statistical significance of the 10 mcg estradiol vaginal tablet versus placebo in the improvement of severity was not demonstrated for any of the assessed individual symptoms. Statistically significant improvement versus placebo for the 10 mcg estradiol vaginal tablet was demonstrated for each of the remaining two recommended co-primary endpoints: 1) mean change from baseline to week 12 in the vaginal Maturation Index (proportion of superficial and parabasal cells), and 2) mean change from baseline to week 12 in vaginal pH ($p<0.001$ for both endpoints). However, all three co-primary endpoints must demonstrate a statistically significant difference versus placebo (b)(4). Thus, the data submitted on December 7, 2007 for Phase 3a Study VAG-2195 did not meet efficacy criteria for (b)(4) as defined by the Agency's 2003 Draft HT Clinical Trial Guidance. The supplement was given a complete response regulatory decision in a letter issued on October 15, 2008.

Novo Nordisk requested and was granted a Type A meeting which was held on March 20, 2009. At this meeting, the Sponsor represented that they never understood that their efficacy analyses should assess as a co-primary efficacy variable one or more individual moderate to severe symptoms in addition to the analysis of co-primary variables of vaginal pH and vaginal superficial and parabasal cells. The Sponsor maintained this position despite repeated attempts by the Division to have the Sponsor come in for a preNDA meeting. In a letter dated November 15, 2007, the Division stated, "We continue to strongly recommend that you schedule the suggested preNDA meeting". The letter continues:

> "1. Should you continue to believe that a preNDA meeting is not needed, we are providing you with the following information regarding the Division's current guidance to Sponsors regarding the primary efficacy analysis for the indication of (b)(4) (b)(4)
>
> a. The most bothersome symptom co-primary endpoint should be based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms.
> b. The patient population to be analyzed for the primary efficacy analysis should meet enrollment criteria for (1) vaginal pH (pH greater than 5), (2) vaginal cellular maturation (no greater than 5% superficial cells), and (3) identification of a moderate to severe most bothersome symptom.
> c. We remind you of the information that was provided to you in our communication of February 1, 2005. This information included the following guidance in Item 8: "We do not recommend that a composite symptom score, as proposed, be calculated."
> d. In accordance with our recommendation that a composite symptom score not be used for the co-primary endpoint, your clinical trial should demonstrate that, compared to subjects treated with placebo, subjects treated with Vagifem® 10 µg vaginal tablets have a statistically significant improvement in one or more of the individual symptoms listed in Item 1a above, as well as a statistically significant decrease in vaginal pH, an increase in vaginal superficial cells, and a decrease in vaginal parabasal cells.

2. We are not aware of your having submitted your final Statistical Analysis Plan (SAP) for Study VAG-2195 or your planned NDA. Please submit your SAP for our review and comments prior to submission of your NDA."

In its cover letter to NDA 20-908/SE2-013, Novo Nordisk acknowledged the following:

"As suggested in the communication dated November 15, 2007 from the Agency to the sponsor, the following items have been addressed in this submission.

1a) the most bothersome symptom co-primary endpoint is based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms.

1b) the patient population to be analyzed for the primary efficacy analysis meets the enrollment criteria for (1) vaginal pH (pH greater than 5), (2) vaginal cellular maturation (no greater than 5% superficial cells), and (3) identification of a moderate to severe most bothersome symptom.

1c) as recommended a composite symptom score was not calculated or used as a co-primary endpoint.

1d) as per the Division's recommendations the data were analyzed to demonstrate that subjects treated with Vagifem® 10 µg vaginal tablets as compared to placebo showed statistically significant improvement from baseline to week 12 in:

- the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- lowering of vaginal pH
- vaginal Maturation Index

2) as requested, a Statistical Analysis Plan (SAP) for VAG-2195 is included in this submission."

The Sponsor stated in the March 20, 2009 meeting that they intended to apply for and receive for its 10 mcg estradiol vaginal tablet, the same indication for its currently approved 25 mcg estradiol vaginal product. With the Sponsor's insistence that, despite all of the attempts from the Division to inform them of the level of the information needed to meet the Agency's 2003 Draft HT Clinical Trial Guidance for efficacy in the treatment of one or more moderate to severe most bothersome symptoms, they did not understand that their data did not meet this standard, the Division acknowledged the Sponsor's lack of understanding. The meeting minutes of the March 20, 2009 meeting state, "based on the discussion and clarification provided by Novo Nordisk…the Applicant **may** not have fully understood the intent of the draft Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom" prior to the Division's letter of November, 2007." The Division indicated that the "clinical deficiency regarding the efficacy of Vagifem® (estradiol vaginal tablets) 10 mcg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified primary analysis." "The Division, however, will need to confirm that the Applicant's composite re-analysis for the most bothersome symptom supports a finding that treatment with Vagifem® 10 µg is statistically superior to treatment with placebo."

The Division requested that Novo Nordisk provide the following documents in the sNDA 20-908/SE1-013 re-submission:

- background information and justification for the design and analysis of Study VAG-2195
- the "White Paper" presented by (b)(4) at the March 20, 2009 Type A meeting

- data file(s) to support the protocol-defined primary analysis for the most bothersome symptom and case report forms (CRFs) to confirm the baseline and Week 12 (or last observation carried forward [LOCF] values in the data file(s)
- the final Report (or alternatively, an abbreviated interim final Report) for completed Study VAG-1748 (endometrial safety study)
- proposed product labeling and a safety update as described in the Complete Response letter of October 15, 2008.

On May 26, 2009, Novo Nordisk Inc. submitted a Class 2 re-submission for the 10 mcg estradiol vaginal tablet. The re-submission contained the requested information including a re-analysis of a composite of all most bothersome symptoms, and the final report of a 12-month non-IND safety study (Study VAG-1748).

2. Background

In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1533.37 FR 14826 dated July 31, 1972) which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature found non-contraceptive estrogen drugs to be effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543, 41 FR$#114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows:

1. moderate-to-severe vasomotor symptoms (MSVMS) associated with the menopause;
2. senile vaginitis;
3 kraurosis vulvae;
4. pruritis vulvae;
5. abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology;
6. female hypogonadism;
7. amenorrhea;
8. female castration;
9. primary ovarian failure;
10. prevention of postpartum breast engorgement;
11. palliation of selected cases of inoperable progressing mammary and prostatic carcinoma; and
12. postmenopausal osteoporosis.

On September 29, 1976, Federal Register notice 41 FR 43108 instituted "class labeling" for estrogen products. The purpose was to introduce uniform labeling with respect to benefits and risks of these products. Prior to 1999, the indication of treatment of vulvar and vaginal atrophy was granted to drug products as part of non-contraceptive estrogen class labeling for products that demonstrated efficacy for the treatment of moderate to severe vasomotor symptoms. On September 22, 1999, draft revision of the LABELING GUIDANCE FOR NON-CONTRACEPTIVE ESTROGEN DRUG PRODUCTS-PRESCRIBING INFORMATION FOR HEALTH CARE PROVIDERS AND PATIENT LABELING was noticed in 64 FR number 186. This Labeling Guidance specified that indications for estrogen and estrogen/progestin drug products would not be granted (b)(4) would be granted based on clinical trial demonstration of efficacy Subsequent to this notice, the indication for treatment of vulvar and vaginal atrophy was granted based on demonstration of statistically significant improvement in the maturation index (vaginal superficial, intermediate and parabasal cells) from baseline to study end for the drug product when compared to placebo. On October 18, 1999, the Advisory Committee on Reproductive Drugs recommended that the Division evaluate drug product efficacy based on demonstration of symptomatic relief in addition

to changes in the signs of vulvar and vaginal atrophy. Keeping this sound advice in-mind, when the Division drafted an updated and revised Guidance for Industry for products intended to treat vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, the 2003 Draft HT Clinical Trial Guidance, we recommended that to be considered efficacious for the indication, a drug product should be studied in a trial where subjects display at baseline at least one moderate to severe symptom of vulvar and vaginal atrophy self described by the patient as most bothersome to her as well as the physical findings consistent with vulvar and vaginal atrophy (pH≥ 5.0 and vaginal smear superficial cells < 5%). To be considered efficacious, products when compared to placebo, should demonstrate statistically significant improvement in the subject's self-identified most bothersome moderate to severe symptom (reduction in severity), vaginal superficial (increase in percentage) and parabasal (reduction in percentage) cells and vaginal pH (reduction).

3. Chemistry Manufacturing Controls (CMC) /Devise

There were no major CMC deficiencies or points of controversy in the original supplement 13 review cycle. The reader is referred to the CMC review of April 30, 2008 for the original review cycle. The CMC review of the re-submission dated November 2, 2009 focused on the container and carton labeling. There was no new CMC information in the re-submission (clarified in a review addendum, dated November 18, 2009. The CMC review concurred with the comments provided by the Division of Medication Error Prevention and Analysis to the Sponsor (see Labeling section 12 of this review). The comments as addressed per the Sponsor were acceptable and the carton and container labeling is acceptable from a CMC perspective.

The Office of New Drug Quality Assurance/ Division of Post-Marketing Evaluation (ONDQA-DPE) concludes that adequate information has been provided to support this supplement. The supplement is recommended for approval.

Recommendations from the Division of Medication Error Prevention and Analysis (DMEPA) on the carton and container labeling are addressed at the end of this review.

4. Nonclinical Pharmacology/Toxicology

This is a lower dose of the previously approved drug product Vagifem®. No new nonclinical pharmacology or toxicology studies were performed and none were requested. No new pharmacology/toxicology information was provided in the complete response. Refer to the Nonclinical Pharmacology and Toxicology review of May 21, 2008 from the original review cycle and the brief review for the complete response dated November 9, 2009.

5. Clinical Pharmacology/Biopharmaceutics

See the Clinical Pharmacology Primary Review of sNDA 20-908/SE1-013, dated July 17, 2008, for a detailed discussion of Phase 1 Study VAG-1850. See also the Clinical Pharmacology Re-Submission Review dated October 15, 2009 and Clinical Pharmacology Review Addendum dated November 18, 2009. No new information from a Clinical Pharmacology/Biopharmaceutics standpoint was submitted with the complete response.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed the Clinical Pharmacology related sections of the proposed product labeling in this re-submission for NDA 20-908 / S-013 submitted on May 26, 2009, July 9, 2009, September 18, November 12, 2009 and November 18, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable. There were no outstanding Clinical Pharmacology issues following the concurrence between the Sponsor and the Division on the final agreed upon label.

Clinical Pharmacology comments were provided to the Sponsor with the exception of the recommendation to remove the Nursing Women information from the SPECIFIC POPULATIONS section of the Highlights and Full Prescribing Information and the *Pregnancy* information from USE IN SPECIFIC POPULATIONS. The clinical team disagrees with this recommendation because even though the label indication is for postmenopausal women, this class of product is frequently used off label for perimenopausal women for relief of menopause related symptoms and for reproductive age women in ART. Pregnancy is a possibility in both of these populations and thus the safety information related to pregnancy and lactation are important for the label to address. The Sponsor appropriately addressed all other comments from the Clinical Pharmacology reviewer.

6. Clinical Microbiology:

Drug product specifications for the 10 mcg vaginal tablets were based on similarity to the 25 mcg tablet. Tests listed in the drug product specification for the 10 mcg tablet are the same as for the approved 25 mcg estradiol tablet. No other information was provided in the complete response submission.

7. Clinical /Statistical Efficacy

See the Medical Officer's Primary Review dated October 6, 2008 and the Statistical Review dated October 8, 2008 for a detailed description of the efficacy data submitted, either in the original submission or upon request of DRUP, and reviewed during the first review cycle. See also the Medical Team Leader's Review dated October 7, 2008 and the Division Director's Review dated October 14, 2008.

A single randomized, double-blind, multi-center, placebo-controlled, parallel-group, clinical trial provided the primary efficacy data in support of this NDA. Per the 2003 Draft HT Clinical Trial Guidance, clinical trials for treatment of the moderate to severe symptoms of vulvar and vaginal atrophy should demonstrated a reduction in the mean severity of the moderate to severe symptom that the subjects has self-identified as most bothersome **and** reduction in the vaginal pH **and** reduction in the proportion of parabasal cells on vaginal cytology smear **and** increase in superficial cells on vaginal cytology smear. In addition, the 2003 Draft HT Clinical Trial Guidance recommends study participants be enrolled who have self-identified at least one moderate to severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.

In the original submission, the Division analyzed the data submitted by the Sponsor in accordance with the 2003 Draft HT Clinical Trial Guidance for treatment of moderate to severe symptoms of vulvar and vaginal atrophy. The Divisions analyses addressed two populations of interest, those meeting at baseline, all criteria for vulvar and vaginal atrophy as specified in the preceding paragraph (mITT-1) and those meeting only the symptom criterion at baseline (mITT-2). The results of the analyses of the two populations for the symptom co-primary endpoint are presented in the following Table 1.

Table 1. FDA Final Analyses of Mean Change from Baseline to Week 12 in the Individual Moderate to Severe Symptom of Vulvar and Vaginal Atrophy Identified as Most Bothersome at Baseline. mITT-1 and mITT-2 Population.

Vulvar and Vaginal Atrophy Symptom	10 mcg Estradiol Vaginal Tablet	Placebo	10 mcg Estradiol Vaginal Tablet	Placebo
	mITT-1 Analyses[1]		mITT-2 Analyses[2]	
Dyspareunia				
n	76	46	89	52
mean change from baseline	-1.26	-0.89	-1.21	-0.96
p-value vs. placebo	0.0200		0.1164	
Dryness				
n	36	22	52	25
mean change from baseline	-1.40	-0.91	-1.35	-0.92
p-value vs. placebo	0.0929		0.2207	
Irritation				
n	21	6	22	7
mean change from baseline	-1.33	-1.00	-1.32	-1.14
p-value vs. placebo	0.7140		0.8352	

[1]mITT-1 = modified intent to treat analyses with population consisting of all subjects who were randomized and at baseline met the criteria of at least one most bothersome moderate to severe symptom, vaginal pH greater than or equal to 5, less than 5% superficial cells on a vaginal smear.
[2]mITT-2 = modified intent to treat analyses with population consisting of all subjects who were randomized and at baseline met the criteria of at least one most bothersome moderate to severe symptom.

When subject to the appropriate Bonferroni statistical adjustment for multiple comparisons (p-value should be less than 0.016 to be considered statistically significant), the FDA analyses do not indicate a statistically significant improvement in favor of the 10 mcg estradiol vaginal tablet over placebo in the severity of any of the evaluated individual most bothersome moderate to severe symptoms. The analyses for the co-primary variables of change from baseline for vaginal pH and change from baseline for vaginal superficial cells and vaginal parabasal cells demonstrated a statistically significant improvement for the 10 mcg estradiol vaginal tablet versus placebo for both mITT populations. However, as has been previously stated in this review, for a [redacted](b)(4) claim, all three co-primary variables must be satisfied.

The Division requested that the Sponsor submit background information and justification for the design and analysis of Study VAG-2195 and the data file(s) to support the protocol-defined primary analysis for the most bothersome symptom and case report forms (CRFs) to confirm the baseline and Week 12 (or last observation carried forward [LOCF] values in the data file(s). The May 26, 2009 re-submission presented the original protocol specified analysis of a composite of all most bothersome symptoms, between baseline and week 12, for the 10 mcg estradiol vaginal tablet versus the placebo vaginal tablet. This analysis was similar to that presented in the original NDA for the 25 mcg estradiol vaginal tablet for the treatment of atrophic vaginitis (that analysis looked at a composite score of three symptoms). The analysis for the low dose estradiol vaginal tablet demonstrates a statistically significant difference (p=0.002) in the mean change from baseline for the 10 mcg estradiol vaginal tablet compared to the placebo vaginal tablet at week 12 (LOCF). See Table 2 which is adapted from the Medical Officer Review (Table 2), the Statistical Review (Table 1) and the re-submission re-analysis.

Table 2: Mean Change from Baseline to Week 12 in a Composite of Most Bothersome Symptoms Compared to Placebo – ITT Population[a] – Study VAG-2195

Visit	10 mcg Estradiol Vaginal Tablet		Placebo Vaginal Tablet		p-value[b]
	N	Mean	N	Mean	
Baseline	190	2.36	93	2.29	-
Change from Baseline to Week 12 (LOCF)	190	-1.20	93	-0.84	0.002

[a] All randomized subjects who received at least one dose of study drug and had at least one post-baseline efficacy evaluation.
[b] ANCOVA with treatment effect and baseline values as a covariate in the model

8. Safety

See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of the safety evaluations and findings in 52-week, Phase 3a, Study VAG-2195 and supportive Phase 1 Study VAG-1850.

The key safety endpoint evaluated in Study VAG-2195 was the evaluation of the hyperplasia rate, as assessed from endometrial biopsy at the end of 12-monts of study. Other assessments include: vital signs, physical examination, gynecological examination, papanicolaou cervical smear, transvaginal ultrasound, blood laboratory determinations and adverse events.

No deaths occurred in Study VAG-2195. Seven (7) subjects (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [5 of 205 treated subjects = 2.4%] and 2 subjects in the placebo vaginal tablet treatment group [2 of 103 treated subjects = 2%.]) in Study VAG-2195 reported serious adverse events (SAEs).

In Study VAG-2195, all subjects had a uterus and by protocol were to have an endometrial biopsy performed at screening and at the end-of-study (52 weeks) or early termination provided the subjects had been treated for 3 months or longer. Subjects with endometrial hyperplasia or cancer at screening biopsy were excluded from the study. One hundred and seventy-two subjects (172 of 205 treated subjects = 84%) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study endometrial biopsy performed in Study VAG-2195. Seventy-nine subjects (79 of 103 treated subjects = 77%) in the placebo vaginal tablet treatment group had end-of-study endometrial biopsies performed. At 52 weeks 18% of subjects treated with the 10 mcg estradiol vaginal tablet and biopsied had no tissue, 24% had insufficient tissue, 38% had atrophic endometrium, 15% had inactive endometrium, and 0% had proliferative, secretory or menstrual type endometrium. One subject was noted to have complex hyperplasia without atypia (subject (b)(6) was diagnosed on day 43 and received less than 9 days of treatment,) and one subject was noted to have endometrial carcinoma (subject (b)(6) diagnosed on study day 326). Unopposed treatment with estrogen is a known risk for development of endometrial hyperplasia and cancer. The 0.5% rate of endometrial hyperplasia is low and the combined 1% rate of endometrial hyperplasia + endometrial cancer demonstrated in VAG-2195 is not high when considering that this is an estrogen-only product.

On April 3, 2008, Novo Nordisk submitted the 4-Month Safety Update. There were no new safety data from completed studies VAG-2195 and VAG-1850 reported since the 120-Day Safety update submitted April 3, 2008 during the first review cycle.

The May 26, 2009 re-submission contained the final clinical trial report for completed non-IND Study-1748 entitled "A 12-month open label multicenter trial to investigate the endometrial safety of Vagifem® Low Dose (10 µg 17beta-estradiol tablet) in postmenopausal women with atrophic vaginitis symptoms". Study VAG-1748 was conducted in the Czech Republic, Denmark, Finland, France, Hungary, Norway, and Sweden to support the registration of 10 mcg estradiol vaginal tablets in Europe. The primary safety endpoint was the hyperplasia rate at the end of study (Week 52). Endometrial biopsies were taken at the beginning and end of the study." One death had been reported in Study VAG-1748 (Subject (b)(6), 77 years of age, treatment with 10 mcg estradiol vaginal tablets from (b)(6) until (b)(6), France). In (b)(6) (b)(6) Subject (b)(6) was diagnosed with cerebral metastasis of a primary unknown cancer. The subject died on (b)(6) An autopsy was not performed. The event was assessed as "unlikely related" to study medication by the investigator and the Sponsor. Fourteen (14) subjects experienced SAEs in non-IND Study VAG-1748 (4.2%, 14 of 336 subjects treated with 10 mcg estradiol vaginal tablets). These include: subject (b)(6) with abdominal pain (small intestine enteritis), hypokalemia and anemia; subject (b)(6) with melena; subject (b)(6) with a cholecystectomy for cholelithiasis; subject (b)(6) with a fracture of the right wrist (radius and ulna, distal); subject (b)(6) with fracture of the left wrist (radius); subject (b)(6) with a hematoma and post-operative infection following abdominal plastic surgery; subject (b)(6) with back pain from spinal stenosis and subject (b)(6) with recurrence of leukemia to the neck.

In Study VAG-1748 all subjects had a uterus and were to have had an endometrial biopsy performed at screening and at the end-of-study or early termination provided the subjects had been treated for 3 months or longer. Subjects with endometrial hyperplasia or cancer at screening were excluded from the study. Transvaginal ultrasound (TVU) assessments were conducted preceding the endometrial biopsy. An evaluable endometrial biopsy at screening was defined as "endometrial tissue sufficient for diagnosis". Per the study protocol, if no tissue was obtained at screening the biopsy could be repeated. Endometrial biopsies with insufficient tissue for diagnosis and TVU double-wall thickness < 4 mm could be categorized as "atrophic endometrium".

Endometrial tissue obtained was "processed in the same manner by a central laboratory". Two independent pathologists blinded to treatment and time of biopsy assessed each endometrial sample. In case of disagreement between the two pathologists, a third blinded pathologist adjudicated the final histologic determination. The Agency's 2003 Draft HT Clinical Trial Guidance recommended histologic characteristics of the endometrium were followed.

One hundred and seventy-two subjects (84%, 172 of 205 treated subjects) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study endometrial biopsy performed in Study VAG-1748. Seventy-nine subjects (77%, 79 of 103 treated subjects) in the placebo vaginal tablet treatment group had end-of-study endometrial biopsies performed. At end-of-study 7.4% of subjects treated with the 10 mcg estradiol vaginal tablet and biopsied had no tissue, 29.9% had insufficient tissue, 47.9% had atrophic endometrium, 13.7% had inactive endometrium, and <1% had proliferative, 0% had secretory or menstrual type endometrium. One subject ((b)(6) was entered into the study with a screening finding of unsatisfactory for diagnosis and limited surface endometrium present. A TVU noted a 2.0 mm endometrium. Her end-of-study endometrial biopsy was reported by pathologist 1 and 2 as "tissue volume too scant for diagnosis- no endometrium present, normal ectocervical and endocervical tissue" and "unsatisfactory for diagnosis-limited surface endometrium present", respectively. The absence of endometrial tissue triggered a protocol-specified repeat endometrial biopsy. The histological results were read by three blinded pathologists as follows:

Pathologist 1 =	Endometrial hyperplasia, complex type (no atypia), epithelial metaplasia, mucinous type
Pathologist 2 =	Polyp, hyperplastic type, epithelial metaplasia, papillary mucinous type (no atypia)
Pathologist 3 =	Endometrial hyperplasia, complex type (no atypia)

A fractionated "abrasion" (curettage) was performed on (b)(6). The histology report was read as "endocerv. epithelium without evidence of atypical cells and ex-mucous membrane without evidence of atypical cells-no evidence of endometrium. The investigator determined that the diagnosis of endometrial hyperplasia was not confirmed and, therefore, the biopsy report was to be considered a false positive. The Division's clinical team does not agree with this determination. A finding of endometrial hyperplasia can not be ignored based on failure to replicate the finding at dilatation and curettage. Focal hyperplasia may be completely removed by the original biopsy. The clinical team determines that this should be counted as endometrial hyperplasia. One case of endometrial hyperplasia following 52-weeks of treatment with an estrogen-alone product does not raise concern. The percentage of women reporting vaginal bleeding in Study VAG-1748 was low and acceptable for a 52-week study.

The endometrial safety findings from VAG-2195 and Study VAG-1748 support that the use of estrogen class labeling for the 10 mcg estradiol vaginal tablet is appropriate. Estrogen-only products have a Black Box Warning which identifies adequate diagnostic measures to be taken in users with persistent or recurring abnormal vaginal bleeding and advises the addition of a progestin to estrogen therapy to reduce the risk of endometrial hyperplasia.

In addition to the safety findings noted above, no significant changes in vital signs were noted in the two 52 week studies, VAG-2195 and VAG-1748. In Study VAG-2195, there were no clinically relevant differences from normal reference ranges or from screening values for any of the laboratory assessments performed for either the 10 mcg estradiol vaginal tablet treatment group or the placebo vaginal tablet treatment group. In Study VAG-1748, 13 subjects experienced 17 laboratory abnormalities reported as treatment emergent adverse events. These included increases in alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, serum cholesterol and lipids as well as decreased in serum potassium and B12. These 13 subjects represented less than 1 % of subjects.

Overall, the safety profile as presented in the integrated summary of safety is acceptable and is not sufficiently different from previously approved estrogen-only products (including the 25 mcg dose of Vagifem®) to raise any additional concerns.

9. Advisory Committee

There were no controversial or difficult issues requiring input beyond that of the Agency reviewers from an Advisory Committee.

10. Pediatrics

Refer to decision in the original review cycle. The Sponsor requested a full waiver from the requirement to assess the safety and effectiveness of Vagifem® vaginal tablet in all relevant pediatric subpopulations in accordance with 21 CFR 314.55(c)(2). The rationale for this request is that (b)(4) does not occur in pediatric patients and, therefore, use of this product prior to menarche is not indicated.

In an electronic mail communication dated May 15, 2008, the Pediatric and Maternal Health Division in the Office of New Drugs indicated that they concurred with the waiver.

11. Other Relevant Regulatory Issues

See reference to the Division of Scientific Investigation's recommendation during the original review cycle that based on its inspection of clinical trial sites that the clinical trial data is acceptable for review

The Medical Officer determined in the original review cycle that the Sponsor disclosed financial arrangements with clinical investigators were consistent with the recommendation by the Agency in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. No clinical investigator disclosed any "propriety interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b)" and "no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

12. Labeling

Labeling negotiations were fairly straightforward. The 10 mcg dose received the same estrogen class labeling as the originally approved dose of 25 mcg. The main differences of opinion and discussion topics for labeling were:

- The presentation of the efficacy data for the original 25 mcg. The Division requested that this data be presented not in the form of a figure as in the original label, but in tabular form to make it consistent with PLR recommendations for other HT products. The tabular presentation is for the mean change from baseline to Week 7 (LOCF) and Week 12 (LOCF) in a composite score of symptoms for the group taking the 25 mcg estradiol tablet versus placebo for the ITT population.
- The use of the descriptive term estradiol instead of 17-beta estradiol as proposed by the Sponsor. ONDQA has provided in the Description section identification of estradiol hemihydrate. By convention the remainder of the label refers only to drug substance as estradiol.
- The notation of a case of complex endometrial hyperplasia as an adverse endometrial effect for Study VAG -1748. As noted above in this review one subject in Study VAG-1748 was found to have complex endometrial hyperplasia on endometrial biopsy as read by two pathologists. The finding was not replicated on dilatation and curettage and the investigator determined that the original biopsy was a false positive diagnosis. The clinical team re-adjudicated this finding as endometrial hyperplasia and indicated that it should be included in the label.

This reviewer also notes the following consultative recommendations:

Division of Risk Management (DRISK):

- For consistency, we suggest adding the Patient Instructions for Use that appear in the original PPI to the PI. The PPI and PI should have consistent information.
- We suggest moving the instructions to the end of the PPI to be consistent with other patient labeling materials.
- We recommend including information on 10 mcg dosing and scheduling and on the number of doses in each carton, if this is different from the information provided for the 25 mcg dose.
- We added the following statement to the end of the section, "General information about the safe and effective use of Vagifem."

"Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."
This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse events on Labeling for Human Drug Products in Federal Register Vol. 73, No.2, p.402-404, 1/3/2008).

Office of Surveillance and Epidemiology – Division of Adverse Event Analysis:
The review of data mining scores and the search of the AERS database for Vagifem® did not identify any unlabeled adverse event terms for consideration as additions to the proposed labeling

Division of Medication Error Prevention and Analysis:
Based upon our assessment of the labels and labeling, DMEPA identified the following areas of needed improvement.

1. Replace all unit designations expressed as "µg" with "mcg" when expressed with a strength to be consistent with FDA's policy on excluding dangerous abbreviations and symbols from approved labels and labeling. FDA launched a campaign on June 14, 2006 warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g. trailing zeros).
2. Consider revising the carton labeling so that the (b)(4) (b)(4) (b)(4) In its current location, it may be more difficult to locate the sistent from what consumers and healthcare practitioners are used to.
3. List the inactive ingredients on the carton labeling per 21 CFR 201.100 (b)(5).
4. The numbering in the patient labeling for the instructions is confusing in presentation and the figures are not coordinated with the text. Consider labeling figures alphabetically and reserve the numbers for the instruction steps.

Consult recommendations were communicated to the Sponsor who made the request consult recommendations.

The final agreed upon label is appended to this review.

13. Recommendations/ Risk Benefit Assessments

Prior to 1999, the indication of treatment of vulvar and vaginal atrophy was granted to drug products as part of non-contraceptive estrogen class labeling for products that demonstrated efficacy for the treatment of moderate to severe vasomotor symptoms. In September 1999, the Agency issued a draft revision of the LABELING GUIDANCE FOR NON-CONTRACEPTIVE ESTROGEN DRUG PRODUCTS-PRESCRIBING INFORMATION FOR HEALTH CARE PROVIDERS AND PATIENT LABELING (64 FR number 186) that specified that indications for estrogen and estrogen/progestin drug products would no longer be granted based on class labeling and would be granted based on clinical trial demonstration of efficacy for the requested indication. Subsequent to this notice, the indication for treatment of vulvar and vaginal atrophy was granted largely based on demonstration of statistically significant improvement in the maturation index (vaginal superficial, intermediate and parabasal cells) from baseline to study end for the drug product when compared to placebo. The original approval of Vagifem® (1999) for the 25 mcg vaginal estradiol tablet was unique for products approved at that time for the treatment of atrophic vaginitis in that Vagifem® presented data from a placebo-controlled trial to

support its efficacy (ironically this application also included a symptom component in its assessment of efficacy).

In October 1999, the Advisory Committee on Reproductive Drugs recommended that the Division evaluate drug product efficacy based on demonstration of symptomatic relief in addition to changes in the signs of vulvar and vaginal atrophy. The Division followed the Committee's advice when we drafted an updated and revised Guidance for Industry for products intended to treat vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause. The 2003 Draft HT Clinical Trial Guidance recommends that to be considered efficacious for the indication, a drug product should be studied in a trial with a population of subjects that display at baseline one moderate to severe symptom of vulvar and vaginal atrophy that they self-describe as most bothersome as well as the physical findings consistent with vulvar and vaginal atrophy (pH≥ 5.0 and vaginal smear superficial cells < 5%). To be considered efficacious, products when compared to placebo, should demonstrate statistically significant improvement in the subject's self-identified most bothersome moderate to severe symptom (reduction in severity), vaginal superficial (increase in percentage) and parabasal (reduction in percentage) cells and vaginal pH (reduction).

Based on failure of the data in the original December 2007 efficacy supplement to meet the Agency's 2003 Draft HT Clinical Trial Guidance recommendations on efficacy (b)(4) (b)(4) I concurred with the recommendations of the primary clinical and statistical reviewers that the 10 mcg estradiol vaginal tablet not be approved for this indication. The Division Director likewise concurred and, subsequently, a complete response action was taken on October 15, 2008

The Sponsor protested the Division's decision. After the post-decisional discussion with the Sponsor, the Division considered the possibility that the Sponsor did not grasp, prior to submission of their NDA, that they would be expected to demonstrate efficacy in all co-primary endpoints: one or more moderate to severe most bothersome symptoms, vaginal pH and vaginal superficial and parabasal cells. Novo Nordisk indicated that it had been their intention only to provide an option of a lower dose estradiol vaginal product for the same indication as their currently approved 25 mcg vaginal product. The Division in acknowledging the Sponsor's confusion offered as a path forward to have the Sponsor submit the original "protocol-specified" composite of most bothersome symptoms as a co-primary endpoint for the indication of treatment of atrophic vaginitis, the indication of the currently approved Vagifem® product.

The data provided in the Sponsor's complete response still do not support an indication for (b)(4) claim. However, I can align with the opinion that the data provided for the low dose 10 mcg estradiol vaginal tablet rises to the same level of "proof of efficacy" as established in the original approval for Vagifem® 25 mcg dose. It is, however, my opinion that in this present day, the granting of this indication has to be reserved for this specific instance of a lower dose option of a product with a pre-existing indication of atrophic vaginitis. This indication is, in my opinion, not appropriate for a new product or an existing product seeking a new indication of (b)(4). Atrophic vaginitis is, in my opinion, a historical indication and, thus, it should be considered as such and relegated to the past. The Division has pursued an updated approach to (b)(4) and has determined based on strong external input that the granting of this indication must be strongly anchored to the relief of the individual symptom(s). New products must be considered under this paradigm and the indication of treatment of atrophic vaginitis based on assessment of composite of symptoms (without demonstration of relief of any one or more individual symptom) with assessment of pH and vaginal cells is not appropriate. The Division has been consistently

providing recommendations to Sponsors [redacted] (b)(4) We must not retreat from this position. Should approval be granted for this lower dose of an approved product with an existing indication, it must not be used as precedent for new products to follow.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHELLEY R SLAUGHTER
11/20/2009

Cross-Discipline Team Leader Review

Date:	October 7, 2008
From:	Shelley R. Slaughter, M.D., Ph.D.
NDA:	20-908/SE2-013
Applicant:	Novo Nordisk, Inc,
Date of Submission:	December 7, 2007
PDUFA:	October 7, 2008
Requested Proprietary Name/	Vagifem®
Established (USAN) name:	estradiol vaginal tablet
Dosage forms/Strength:	10 mcg estradiol vaginal tablet
Regimen:	one tablet inserted intravaginally daily for two weeks followed by one tablet inserted intravaginally twice weekly continuously
Proposed Indication:	(b)(4) (source: Form 356h)
Recommendation:	Should not be approved. The data included in supplement failed to demonstrate efficacy for estradiol vaginal tablet for the (b)(4).

Executive Summary:

1. Introduction

With this efficacy supplement, Novo Nordisk is seeking an indication of (b)(4) (b)(4) for a lower dose (10 mcg) of its approved product Vagifem (currently 25 mcg estradiol vaginal tablet). The supplemental application is supported by a single placebo-controlled, Phase 3 efficacy and safety study and a Phase 1 pharmacokinetic and safety study. The safety profile of the 10 mcg estradiol vaginal tablets did not identify any new safety signals. Unopposed estrogen is known to be causally associated with endometrial cancer and previous published 12 month or longer trials have shown 1 or more endometrial cancers in unopposed estrogen arms. Because of this known risk of unopposed estrogen, "Estrogen Class" labeling for all approved estrogen-alone products, carries a Black Box Warning which identifies adequate diagnostic measures to be taken in users with persistent or recurring abnormal vaginal bleeding. The Black Box Warning also advises that the addition of a progestin to estrogen therapy reduces the risk for endometrial cancer. Should this product gain approval, in this or future review cycles, it would be appropriate for it to receive Estrogen Class labeling and the same Black Box Warning.

The overriding review concern for supplement 13 was the efficacy of the drug product. The 2003 Draft Guidance for Industry entitled, "ESTROGEN AND ESTROGEN/PROGESTIN DRUGS PRODUCTS TO TREAT VASOMOTOR SYMPTOMS AND VULVAR AND VAGINAL ATROPHY SYMPTOMS – RECOMMENDATIONS FOR CLINICAL EVALUATION" (henceforth referred to in this review as the 2003 Draft HT Clinical Trial Guidance) recommends that for a non-new molecular entity seeking the indication of (b)(4) (b)(4), a single clinical trial be conducted that demonstrates for the drug product vs. placebo statistically significant improvement in the co-primary endpoints of: mean change (i.e. reduction in severity) in **the** (*intended as individual*) moderate to severe most bothersome symptom; mean change (increase)in vaginal superficial and vaginal parabasal cells (decrease) obtained from a smear of the lateral vaginal wall and mean change (reduction) in the vaginal pH. The 2003 Draft HT Clinical Trial Guidance further recommends that the population to be randomized to trials for symptoms of vulvar and vaginal atrophy, be composed of women who at

baseline meet the criteria of at least one moderate to severe symptom of vulvar and vaginal atrophy that the woman (not the physician) has identified as most bothersome to her, a vaginal ph greater or equal to 5 and less than 5% superficial vaginal cells on the smear.

Some Sponsors have initially confused the guidance document recommendation for the symptom co-primary and have proposed a composite of all most bothersome symptoms. This is not the intent of the 2003 Draft HT Clinical Trial Guidance. In the IND/pre-NDA stages, the Division of Reproductive and Urologic Products (subsequently referred to in this review as DRUP or the Division) has been careful to provide Sponsors further clarification that they should analyze each individual moderate to severe most bothersome symptom sought and not a composite. In a teleconference between the Division (Senior Regulatory Health Project Manager) and the Sponsor on September 18, 2007, DRUP conveyed to Novo Nordisk the recommendation that Novo Nordisk request a preNDA meeting for the 10 mcg estradiol vaginal tablet product. In a letter dated November 15, 2007, the Division stated, "We continue to strongly recommend that you schedule the suggested preNDA meeting". The letter continues:

> "1. Should you continue to believe that a preNDA meeting is not needed, we are providing you with the following information regarding the Division's current guidance to Sponsors regarding the primary efficacy analysis for the indication of (b)(4) (b)(4)
>
> a. The most bothersome symptom co-primary endpoint should be based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms.
> b. The patient population to be analyzed for the primary efficacy analysis should meet enrollment criteria for (1) vaginal pH (pH greater than 5), (2) vaginal cellular maturation (no greater than 5% superficial cells), and (3) identification of a moderate to severe most bothersome symptom.
> c. We remind you of the information that was provided to you in our communication of February 1, 2005. This information included the following guidance in Item 8: "We do not recommend that a composite symptom score, as proposed, be calculated."
> d. In accordance with our recommendation that a composite symptom score not be used for the co-primary endpoint, your clinical trial should demonstrate that, compared to subjects treated with placebo, subjects treated with Vagifem 10 μg vaginal tablets have a statistically significant improvement in one or more the individual symptoms listed in Item 1a above, as well as a statistically significant decrease in vaginal pH, an increase in vaginal superficial cells, and a decrease in vaginal parabasal cells.
>
> 2. We are not aware of your having submitted your final Statistical Analysis Plan (SAP) for Study VAG-2195 or your planned NDA. Please submit your SAP for our review and comments prior to submission of your NDA."

Despite the two separate requests that the Sponsor participate in a pre-NDA meeting with the Division, Novo Nordisk did not request such a meeting. As indicated, the November 15, 2007 letter informed the Sponsor not only of the co-primary efficacy endpoints [including looking at the **individual** (not a composite) most bothersome moderate to severe symptom of vulvar and vaginal atrophy] and how they should be analyzed, but also the population to be analyzed in the primary efficacy analyses.

In its cover letter to NDA 20-908/SE2-013, Novo Nordisk acknowledged the following:

"As suggested in the communication dated November 15, 2007 from the Agency to the sponsor, the following items have been addressed in this submission.

1a) the most bothersome symptom co-primary endpoint is based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms.

1b) the patient population to be analyzed for the primary efficacy analysis meets the enrollment criteria for (1) vaginal pH (pH greater than 5), (2) vaginal cellular maturation (no greater than 5% superficial cells), and (3) identification of a moderate to severe most bothersome symptom.

1c) as recommended a composite symptom score was not calculated or used as a co-primary endpoint.

1d) as per the Division's recommendations the data were analyzed to demonstrate that subjects treated with Vagifem® 10 µg vaginal tablets as compared to placebo showed statistically significant improvement from baseline to week 12 in:

- the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- lowering of vaginal pH
- vaginal Maturation Index

2) as requested, a Statistical Analysis Plan (SAP) for VAG-2195 is included in this submission."

Another efficacy review issue for this supplement related to the population to be analyzed. The Division has used as the primary analyses in five or more prior NDAs, analyses of a modified intent-to-treat population (mITT) consisting of all subjects who were randomized, met at baseline all three criteria for a trial of vulvar and vaginal atrophy (at least one moderate to severe symptom of vulvar and vaginal atrophy self described by the patient as most bothersome to her and pH≥ 5.0 and vaginal smear superficial cells < 5%) and took a dose of study drug. In the cover letter as presented above the Sponsor indicated their understanding of the population to be analyzed and further that they had analyzed the population of subjects meeting all three baseline criteria (cytology, pH and moderate to severe most bothersome symptom). Despite their acknowledgement, the Sponsor analyzed a different mITT, which they mis-termed an ITT, consisting of all subjects who were randomized, met only the symptom criteria and took a dose of study drug. Since the primary analyses is a co-primary analyses of 4 endpoints and not an analyses of the symptom only, this reviewer holds that the modified ITT consisting of subjects meeting the baseline criteria for the three components (referred to elsewhere in this review as mITT-1) is the appropriate mITT.

2. Background

In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1533.37 FR 14826 dated July 31, 1972) which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature found non-contraceptive estrogen drugs to be effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543, 41 FR$#114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows:

1. moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause;
2. senile vaginitis;
3 kraurosis vulvae;
4. pruritis vulvae;

5. abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology;
6. female hypogonadism;
7. amenorrhea;
8. female castration;
9. primary ovarian failure;
10. prevention of postpartum breast engorgement;
11. palliation of selected cases of inoperable progressing mammary and prostatic carcinoma; and
12. postmenopausal osteoporosis.

On September 29, 1976, Federal Register notice 41 FR 43108 instituted "class labeling" for estrogen products. The purpose was to introduce uniform labeling with respect to benefits and risks of these products. Prior to 1999, the indication of treatment of vulvar and vaginal atrophy was granted to drug products as part of non-contraceptive estrogen class labeling for products that demonstrated efficacy for the treatment of moderate to severe vasomotor symptoms. On September 22, 1999, draft revision of the LABELING GUIDANCE FOR NON-CONTRACEPTIVE ESTROGEN DRUG PRODUCTS-PRESCRIBING INFORMATION FOR HEALTH CARE PROVIDERS AND PATIENT LABELING was noticed in 64 FR number 186. This Labeling Guidance specified that indications for estrogen and estrogen/progestin drug products would not be granted based on class labeling and would be granted based on clinical trial demonstration of efficacy for the requested indication. Subsequent to this notice, the indication for treatment of vulvar and vaginal atrophy was granted based on demonstration of statistically significant improvement in the maturation index (vaginal superficial, intermediate and parabasal cells) from baseline to study end for the drug product when compared to placebo. On October 18, 1999, the Advisory Committee on Reproductive Drugs recommended that the Division evaluate drug product efficacy based on demonstration of symptomatic relief in addition to changes in the signs of vulvar and vaginal atrophy. Keeping this sound advice in-mind, when the Division drafted an updated and revised Guidance for Industry for products intended to treat VMS and VVA associated with the menopause, the 2003 Draft HT Clinical Trial Guidance, we recommended that to be considered efficacious for the indication, a drug product should be studied in a trial where subjects display at baseline at least one moderate to severe symptom of vulvar and vaginal atrophy self described by the patient as most bothersome to her as well as the physical findings consistent with vulvar and vaginal atrophy (pH≥ 5.0 and vaginal smear superficial cells < 5%). To be considered efficacious, products when compared to placebo, should demonstrate statistically significant improvement in the subject's self-identified most bothersome moderate to severe symptom (reduction in severity), vaginal superficial (increase in percentage) and parabasal (reduction in percentage) cells and vaginal pH (reduction).

3. Chemistry Manufacturing Controls (CMC) /Devise

There were no major CMC deficiencies or points of controversy. The efficacy supplement proposed an additional lower strength tablet, 0.010 mg, that is to be manufactured at a new drug product manufacturing site, Novo Nordisk, C2 site in Maaloev, Denmark, with a scale-up in batch size from (b)(4) to (b)(4) Most of the chemistry, manufacturing and control information provided for the 0.010 mg tablet is the same as approved for the 0.025 mg tablet, including the drug substance manufacturing and controls, drug product manufacturing process and controls, and container/closure system. The approved methods for identification, assay, related substances, and dissolution have been modified and validated for the analysis of both the 0.025 mg and the 0.010 mg tablets.

In addition, the drug product specification has been amended to propose an increase in the limits for related substance and the approved assay method has been amended to change the injection volume. With regard to the acceptance criteria proposed to related substances test in the drug product specification proposed for the 10 mcg tablet manufactured at the proposed site, the acceptance criteria are not supported by data. The limits approved in the NDA should be retained by the 0.010 mg tablet.

Batch release and stability data to 24 months/25C/60% RH, to 12 months/30C and to 6 months/40C are provided for three production batches manufactured at the proposed Maaloev Denmark site. The data show that the 0.010 mg batches meet the approved drug product specification and are comparable to the approved tablets. The Office of Compliance finds the proposed site acceptable. Both clinical studies, VAG-1850 and VAG-2195 used the 0.010 mg tablets manufactured at the proposed Maaloev Denmark site.

The environmental assessment is acceptable.

The Office of New Drug Quality Assurance/ Division of Post-Marketing Evaluation (ONDQA-DPE) concludes that adequate information has been provided to support this supplement. The supplement is recommended for approval.

4. Nonclinical Pharmacology/Toxicology

This is a lower dose of the previously approved drug product Vagifem®. No new nonclinical pharmacology or toxicology studies were performed and none were requested.

5. Clinical Pharmacology/Biopharmaceutics

Bioavailability (BA) study VAG-1850 was submitted along with efficacy and safety clinical trial VAG-2195. Study VAG-1850 explored the systemic absorption of E_2 from the 10 and 25 mcg dose formulation. Novo Nordisk is seeking to replace the BA data of the 25 mcg dose in the current label with the new systemic absorption data for both the 10 and 25 mcg doses from this trial. The E_2 drug substance and inactive excipients in the 10 mcg dose of Vagifem® are the same as those in the 25 mcg dose of Vagifem® except for the reduction of E_2 (b)(4) (b)(4).

Repeat dosing of 10 mcg of Vagifem® was found to display an E_2 PK profile that was globally similar in pattern to that following 25 mcg administration. Mean plasma concentrations of E_2, E_1, and E_1S were consistently lower for the Vagifem® 10 mcg tablet than the currently-marketed Vagifem® 25 mcg formulation. The mean E_2 plasma concentration over 24 hr were below 11 and 21 pg/ml for Vagifem® 10 and 25 mcg, respectively, after 1, 14 and 83 days of daily administration.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) finds the overall Clinical Pharmacology data NDA 20-908/SE2-013 to be acceptable.

6. Clinical Microbiology:

The drug product specification for the 10 mcg estradiol vaginal tablet is proposed based on the similarity of the 10 mcg estradiol vaginal tablet to the 25mcg estradiol vaginal tablet. Tests listed in the drug product specification are the same as those for the approved 25 mcg estradiol tablet. In addition, the microbiology limits comply with the acceptable (b)(4).

7. Clinical /Statistical Efficacy

A single randomized, double-blind, multi-center, placebo-controlled, parallel-group clinical trial provided the primary efficacy data in support of this NDA. The original trial size was intended to be 600 subjects, 400 in the 10 mcg estradiol vaginal tablet arm and 200 in the placebo arm. Amendment 2, dated February 3, 2006, reduced the sample size from the originally planned 600 to 300, 200 in the 10 mcg estradiol vaginal tablet arm and 100 in the placebo arm. Three hundred nine subjects were randomized in a 2:1 active drug to placebo fashion (205 subjects to the 10mcg estradiol vaginal tablet arm and 104 to the placebo arm). One subject randomized to placebo did not receive study drug leaving 308 subjects who were assessed in the safety cohort.

Per the 2003 Draft HT Clinical Trial Guidance, clinical trials for treatment of the moderate to severe symptoms of vulvar and vaginal atrophy should demonstrated a reduction in the mean severity of the moderate to severe symptom that the subjects has self-identified as most bothersome **and** reduction in the vaginal pH **and** reduction in the proportion of parabasal cells on vaginal cytology smear **and** increase in superficial cells on vaginal cytology smear. In addition the 2003 Draft HT Clinical Trial Guidance recommends study participants be enrolled who have self-identified at least one moderate to severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.

Sponsor Analyses

Per the original December 7, 2007 submission, the efficacy analyses had all been performed on an Intent-to-Treat (ITT) population, defined by the Sponsor as including subjects who received at least one dose of study medication and had baseline and one post-baseline efficacy evaluation. These analyses were in effect not ITT analyses but rather mITT analyses that included all subjects who reported a most bothersome symptom at baseline regardless of the severity of that symptom (i.e. the analyses included *mild* symptoms in addition to moderate and severe symptoms).

On December 27, 2007, the Applicant was requested to provide the following information:

- "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in the percentage of superficial and parabasal cells for the 10 mcg Vagifem and placebo treatment groups (ITT population with LOCF)."

- "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in vaginal pH (ITT population with LOCF)."

- "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in the most bothersome moderate to severe vulvar and vaginal atrophy symptom for each symptom included in the subject self-assessment questionnaire (dryness, irritation, soreness, dysuria, dyspareunia, and bleeding with sexual activity). Include only those subjects who scored the individual symptom as moderate to severe (not mild) and identified the symptom as most bothersome at baseline."

In Response to the Agency's request, the Sponsor provided two additional submissions dated January 25, 2008 and April 17, 2008. The April 17, 2008 submission provided a correction to the

January 25, 2008 submission regarding the total numbers of subjects meeting the Guidance Document requirements of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom. The analyses as submitted by the Sponsor on April 17, 2008 are presented in the tables 1-4.

The Sponsor's presentation of the subject numbers for the mITT population which takes into account, as requested by the Agency, the total numbers of subjects meeting the Guidance Document recommendation for baseline criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom is shown in Table 1.

Table 1. Sponsor Analyses mITT Population (April 17, 2008 submission) Based on FDA Criteria - Number of Subjects Included.

Treatment	**Original Number of Subjects in Sponsor's ITT**	**Number of Subjects Excluded Based on FDA Criteria**	**mITT (Original Sponsor ITT minus Excluded Subjects**
10 mcg estradiol vaginal tablet	204	55	149
Placebo vaginal tablet	102	25	77
Total	306	80	226

Source: sNDA 20-908/SE2-013 Amendment dated April 17, 2008.

The Sponsor's presentation of vaginal maturation for the mITT population which takes into account, as requested by the Agency, the total numbers of subjects meeting the Guidance Document recommendation for baseline criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom is shown in Table 2.

Table 2. Sponsor Analyses mITT Population (April 17, 2008 submission) Based on FDA Criteria – Cellular (Vaginal Superficial and Parabasal) Maturation

Vaginal Cell Cytology	10 mcg Estradiol Vaginal Tablet N= 149	Placebo N=77
Superficial Cells		
baseline mean (SD)	0.5 (1.21)	0.2 (0.61)
n at week 12	146	77
mean change from baseline at week 12	14.7 (16.76)	4.7 (8.04)
p-value vs. placebo	<0.001	
Parabasal Cells		
baseline mean (SD)	47.8 (41.92)	49.8 (41.81)
n at week 12	146	77
mean change from baseline at week 12	-42.5 (45.84)	-10.2 (44.33)
p-value vs. placebo	<0.001	

Source: sNDA 20-908/SE2-013 Amendment dated April 17, 2008

The Sponsor's presentation of vaginal pH for the mITT population which takes into account, as requested by the Agency, the total numbers of subjects meeting the Guidance Document recommendation for baseline criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom is

shown in Table 3. The Sponsor reported the co-primary endpoint variable of pH as a score instead of a pH value. On February 19, 2008, the 74-day filing letter discussed the following with respect to the co-primary endpoint of vaginal pH:

"*Per the Agency's 2003 draft clinical evaluation Guidance for Industry, the mean change in vaginal pH between baseline and week 12 is one of three recommended co-primary endpoints for demonstrating effectiveness in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy. You have not provided an analysis of mean change in vaginal pH between baseline and week 12 as one of the three recommended co-primary endpoints. The submitted mean change calculation based on a calculated vaginal pH score between baseline and week 12 is not acceptable. Provide an analysis of mean change in vaginal pH between baseline and week 12 based on the observed pH values at each time point."*

To collect the pH data the Sponsor utilized a pH strip that corresponded to the following ranges <, 5-5.49, 5.5-6.49 and greater than 6.49. They then applied a scoring system of 0, 1, 2, and 3 corresponding to the previously designated pH range. The pH is reported in the application not as the mean vaginal pH, but rather as a score. In this reviewer's opinion the use of a pH score is not appropriate. The Guidance Document recommends evaluation of mean vaginal pH and not a score. The Sponsor could have utilized pH paper corresponding to whole unit pH values or 0.5 unit pH values and reported the corresponding mean pH values. Unfortunately comments on the Sponsor's method of evaluation of vaginal pH, that is as a score instead of as the actual pH values, were *not* commented upon at the time of the original protocol review. Upon further review (see Appendix – Table Z), it became evident that the source data provided pH as a value and, thus, the Sponsor could have analyzed the mean pH value and not a pH score.

Table 3. Sponsor Analyses mITT Population (April 17, 2008 submission) Based on FDA Criteria – Vaginal pH

	10 mcg Estradiol Vaginal Tablet N= 149	Placebo N=77
Vaginal pH*		
baseline mean (SD)	2.3 (0.67)	2.4 (0.64)
n at week 12	147	77
mean change from baseline at week 12	-1.3 (1.02)	-0.4 (0.77
p-value vs. placebo	<0.001	

Source: sNDA 20-908/SE2-013 Amendment dated April 17, 2008

The Sponsor's presentation of most bothersome moderate to severe symptom for the mITT population which takes into account, as requested by the Agency, the total numbers of subjects meeting the Guidance Document recommendation for baseline criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom is shown in Table 4.

Table 4. Sponsor Analyses mITT Population (April 17, 2008 submission) Based on FDA Criteria – Moderate to Severe Most Bothersome Symptom

Vulvar and Vaginal Atrophy Symptom	10 mcg Estradiol Vaginal Tablet	Placebo
Dyspareunia (pain with sexual activity) n mean change from baseline p-value vs. placebo	 66 -1.30 (0.89) 0.042	 40 -0.95 (0.93)
Dryness n mean change from baseline p-value vs. placebo	 37 -1.38 (0.83) 0.079	 22 -0.91 (0.81)
Irritation n mean change from baseline p-value vs. placebo	 22 -1.27 (0.88) 0.756	 6 -1.00 (0.89)
Soreness n mean change from baseline p-value vs. placebo	 3 -2.00 (1.00)	 0
Bleeding with sexual activity n mean change from baseline p-value vs. placebo	 2 -2.00 (0.00)	 0
Dysuria n mean change from baseline p-value vs. placebo	 1 -1.00 (NA)	 0

Source: sNDA 20-908/SE2-013 Amendment dated April 17, 2008

Per the Sponsor's April 17, 2008 analyses, only for the symptom of dyspareunia did the data demonstrate a statistically significant improvement in the mean severity for the 10 mcg estradiol vaginal tablet vs. placebo. For the symptoms of soreness, bleeding with sexual activity and dysuria, there were too few subjects for meaningful statistical analyses.

FDA Analyses

Based on the information, as submitted in the April 17, 2008, the FDA statistical team arrived at different analyses from those presented by the Sponsor. Per the Statistical Team, the Sponsor's analyses of individual symptoms, as presented above, were performed utilizing ANCOVA under the assumption that the data would be normally distributed. The Agency's statistical team applied a test for normality and determined that the data was not normally distributed and, therefore, non-parametric analyses, ANCOVA on ranks, were the appropriate analyses. On September 22, 2008, the Agency provided Novo Nordisk with the results of the Agency's analyses to that date on the individual most bothersome moderate to severe symptoms of pain with intercourse, vaginal dryness and vaginal irritation (Table 5).

The FDA analyses of the individual most bothersome moderate to severe symptom utilized the mITT population which takes into account only those subjects who were randomized and provided at least one post-baseline assessment and also met the Guidance Document

recommendation for baseline criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom (mITT-1). This reviewer considers this population as the most appropriate for the primary efficacy analyses. This is the population considered in the NDA of other drug products submitted for this indication and used by the Division to confirm efficacy. For complete discussion internally, the Division also analyzed a population with subjects who were randomized and provided at least one post-baseline assessment and who met only part of the Guidance Document baseline recommendation, that being the criterion for a self-identified most bothersome moderate to severe symptom at baseline (mITT-2). These analyses were also provided to the Sponsor and are presented in Table 5. As there was no statistically significant finding, an adjustment for multiple comparisons was not necessary on either the mITT-1 or the mITT-2.

Table 5. FDA Interim Analyses of Mean Change from Baseline to Week 12 in the Individual Moderate to Severe Symptom of Vulvar and Vaginal Atrophy Identified as Most Bothersome at Baseline. mITT-1 and mITT-2 Population.

Vulvar and Vaginal Atrophy Symptom	10 mcg Estradiol Vaginal Tablet	Placebo	10 mcg Estradiol Vaginal Tablet	Placebo
	mITT-1 Analyses[1]		mITT-2 Analyses[2]	
Dyspareunia				
n	73	42	85	48
mean change from baseline	-1.29	-0.93	-1.22	-1.00
p-value vs. placebo	0.0557		0.2018	
Dryness				
n	36	22	49	24
mean change from baseline	-139	-0.91	-1.33	-0.92
p-value vs. placebo	0.0930		0.2290	
Irritation				
n	21	6	22	7
mean change from baseline	-1.33	-1.00	-1.32	-1.14
p-value vs. placebo	0.7140		0.8352	

[1]mITT-1 = modified intent to treat analyses with population consisting of all subjects who were randomized and at baseline met the criteria of at least one most bothersome moderate to severe symptom, vaginal pH greater than or equal to 5, less than 5% superficial cells on a vaginal smear.
[2]mITT-2 = modified intent to treat analyses with population consisting of all subjects who were randomized and at baseline met the criteria of at least one most bothersome moderate to severe symptom.

On September 24, 2008, the Agency had a teleconference with Novo Nordisk to discuss with them why our findings were different from that provided by Novo Nordisk in their April 17, 2008 submission. The Agency supplied the Sponsor with a list of 115 subjects (see Appendix Table X) whom the Agency believed met the criteria for the mITT-1 population for the moderate to severe symptom of dyspareunia which was the only symptom that was disputed between the two sets of analyses (Sponsor vs. Agency). This list of *115* subjects included 9 additional subjects meeting mITT-1 population criteria that were not accounted for in the Sponsor's April 17, 2008 analysis of a total of *106* subjects for dyspareunia. In the September 24, 2008 teleconference, the Division asked the Sponsor to provide it with the list of subjects that Novo Nordisk believes met the criterion to be included in the mITT analysis for dyspareunia.

The Sponsor responded on September 26, 2008 with a list of *122* subjects (see Appendix Table Y) that they newly represented as meeting the baseline criteria (mITT-1 population of subjects with pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom) and providing at least one post-baseline assessment. The primary Medical Officer and the Statistical Team Leader verified this list against the line listings in the original December 07, 2008 submission. Through an independent verification, this reviewer also verified the *122* subjects against the original line listings in the December 07, 2008 submission (see Appendix Table Z). In addition case report forms were viewed for *26* subjects who were either in the Agency's analyses, but not in the Sponsor's or vice versa or for whom there was some discrepancy in the last observation carried forward method of imputing the data. The list of *122* subjects, as presented on September 26, 2008 was agreed upon by the Sponsor and the Agency. On October 1, 2008, the Sponsor submitted an analysis for ANCOVA on ranks for the mean change from baseline on pain with intercourse (the only

individual most bothersome moderate to severe symptom still disputed) for the *122* subjects in the mITT-1 population. This analysis demonstrated a statistically significant p value of 0.017 in the comparison of the 10 mcg estradiol vaginal tablet group vs. placebo group. Similarly, the Sponsor's analysis (submitted October 6, 2008) for ANCOVA on ranks for the Week 12 mean change from baseline on pain with intercourse for the M-2 population of 143 subjects who at baseline met only the criterion of one individual most bothersome moderate to severe symptom, revealed a p-valued of 0.079 for the comparison of the 10 mcg estradiol vaginal tablet group vs. placebo group.

The Agency's final ANCOVA on ranks on the agreed mITT-1 population (see Table 6) for the individual most bothersome moderate to severe symptoms are presented in Table 7.

Table 6. Distribution of Subjects Who Reported Moderate to Severe Symptoms as Most Bothersome at Baseline

Symptoms	Vagifem 2.62		Placebo	
	n	mean	n	mean
Dyspareunia (N=122)	36	2.14	22	2.05
Vaginal Dryness (N=58)	21	2.32	6	2.17
Vaginal Irritation/Itching (N=27)	76	2.62	46	2.63

Table 7. FDA Final Analyses of Mean Change from Baseline to Week 12 in the Individual Moderate to Severe Symptom of Vulvar and Vaginal Atrophy Identified as Most Bothersome at Baseline. mITT-1 and mITT-2 Population.

Vulvar and Vaginal Atrophy Symptom	10 mcg Estradiol Vaginal Tablet	Placebo	10 mcg Estradiol Vaginal Tablet	Placebo
mITT-1 Analyses[1]			mITT-2 Analyses[2]	
Dyspareunia				
n	76	46	89	52
mean change from baseline	-1.26	-0.89	-1.21	-0.96
p-value vs. placebo	0.0200		0.1164	
Dryness				
n	36	22	52	25
mean change from baseline	-1.40	-0.91	-1.35	-0.92
p-value vs. placebo	0.0929		0.2207	
Irritation				
n	21	6	22	7
mean change from baseline	-1.33	-1.00	-1.32	-1.14
p-value vs. placebo	0.7140		0.8352	

When subject to the appropriate Bonferroni statistical adjustment for multiple comparisons (p-value should be less than 0.016 to be considered statistically significant), the FDA analyses do not indicate a statistically significant improvement in favor of the 10 mcg estradiol vaginal tablet over placebo in the severity of any of the evaluated individual most bothersome moderate to severe symptoms.

Based on those subjects who were randomized and provided at least one post-baseline assessment and also met the Guidance Document recommendation for baseline criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified most bothersome moderate to severe symptom (mITT-1), the results indicated an increase in vaginal superficial cells and a decrease in parabasal cells statistically significant ($p<0.001$) in favor of the 10 mcg estradiol vaginal tablet arm compared to placebo. Utilizing the protocol specified scoring system for vaginal pH, the decrease in the mean vaginal pH score was statistically significant in favor of the 10 mcg estradiol vaginal tablet arm compared to placebo.

The 2003 Draft HT Clinical Trial Guidance, recommends that to be considered efficacious, estrogen or estrogen/progestin drug products when compared to placebo, should demonstrate statistically significant improvement in the subject's self-identified most bothersome moderate to severe symptom (reduction in severity), vaginal superficial (increase in percentage) and parabasal (reduction in percentage) cells and vaginal pH (reduction). The data presented in this efficacy supplement met the vaginal superficial cells, vaginal parabasal cells and vaginal pH co-primary criteria for efficacy, [redacted](b)(4), the subject's self-identified most bothersome moderate to severe symptom (reduction in severity).

This reviewer would like to make one additional comment on the data presented to the Agency during the review of this NDA. While it is important to share with the Sponsor differences in the Applicant-presented analyses and those of the Agency, I believe that it is disruptive to have a back and forth exchange between Sponsor and FDA reviewers up to a day before the impending action. The Sponsor presented a total of *4* separate analyses of the same defined population of subjects. This accounting does not include the original analyses presented with the December 7, 2007 submission. It is my belief that the analyses submitted in the application at the time of the original submission by the Sponsor should be their final intended analyses. Analyses should not be allowed to change, at least not multiple times during the course of the review, when there is disagreement with the Agency's analyses. In the final consideration of this application, ***none*** of the analyses (the p-value of 0.020 in the Agency's analyses, the p-value of 0.042 from the Sponsor's April 17, 2008 analyses and the p-value of 0.017 from the Sponsor's revised October 1, 2008 analyses; all of the same mITT-1 population) demonstrated statistically significant superiority of the 10 mcg estradiol vaginal tablet over placebo for any of the most bothersome moderate to severe symptoms of vulvar and vaginal atrophy.

8. Safety

Three hundred nine subjects were randomized via Interactive Voice Response System (IVRS) telephone procedure in a 2:1 active drug to placebo fashion (205 subjects to 10 mcg estradiol vaginal tablets and 104 to placebo). One subject randomized to placebo did not receive study drug leaving 308 subjects who were assessed in the safety cohort. Seventy-five of the 309 randomized subjects (24%) discontinued Study VAG-2195. Of these 75 subjects, 41 were in the 10 mcg estradiol vaginal tablet group and 34 subjects were in the placebo group.

The key safety endpoint evaluated in Study VAG-2195 was the evaluation of the hyperplasia rate, as assessed from endometrial biopsy at the end of 12-monts of study. Other assessments include: vital signs, physical examination, gynecological examination, papanicolaou cervical smear, transvaginal ultrasound and adverse events.

Of the 75 subjects who discontinued Study VAG-2195, 16 (5.2%) discontinued due to adverse events, 17 (5.5%) discontinued because of ineffectiveness of the treatment and 34 (11%) discontinued due to "Other" (personal issues, withdrew consent, lost to follow-up and protocol violations). Those discontinuing due to adverse events was similar between the 10 mcg estradiol

vaginal tablet group (5%, 11 of 205) and the placebo treatment group (4.8%, 5 of 104 subjects). Discontinuation due to ineffective therapy was higher with placebo (10.6%) than with the 10 mcg estradiol vaginal tablet group (2.9%). More subjects in the placebo group (15.4%) compared to the 10 mcg estradiol vaginal tablet group (8.8%) discontinued due to other.

No deaths occurred in Study VAG-2195. Seven (7) subjects (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [5 of 205 treated subjects = 2.4%] and 2 subjects in the placebo vaginal tablet treatment group [2 of 103 treated subjects = 2%.]) in Study VAG-2195 reported serious adverse events (SAEs).

In Study VAG-2195, all subjects had a uterus and had an endometrial biopsy performed at screening and at the end-of-study (52 weeks) or early termination provided the subjects had been treated for 3 months or longer. Subjects with endometrial hyperplasia or cancer at screening were excluded from the study. One hundred and seventy-two subjects (172 of 205 treated subjects = 84%) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study endometrial biopsy performed in Study VAG-2195. Seventy-nine subjects (79 of 103 treated subjects = 77%) in the placebo vaginal tablet treatment group had end-of-study endometrial biopsies performed. At 52 weeks 18% of those subjects biopsied had no tissue, 24% had insufficient tissue, 38% had atrophic endometrium, 15% had inactive endometrium, and 0% had proliferative, secretory or menstrual type endometrium. One subject was noted to have complex hyperplasia without atypia (subject (b)(6) was diagnosed on day 43 and received less than 9 days of treatment,) and one subject was noted to have endometrial carcinoma (subject (b)(6) diagnosed on study day 326). Unopposed treatment with estrogen is a known risk for development of endometrial hyperplasia and cancer. The 0.5% rate of endometrial hyperplasia is low and the combined 1% rate of endometrial hyperplasia + endometrial cancer demonstrated in VAG-2195 is certainly not high when considering that this is an estrogen-only product. Estrogen-only products have a Black Box Warning which identifies adequate diagnostic measures to be taken in users with persistent or recurring abnormal vaginal bleeding and advises that the addition of a progestin to estrogen therapy reduces the risk.

On April 3, 2008, Novo Nordisk submitted the 4-Month Safety Update. As of March 13, 2008, the update reported no new or follow-up safety information for Study VAG-1850 and no new safety information for Study VAG-2195. Follow-up information was available for four subject/five cases.

The 4-Month Safety Update provided initial information on an ongoing European safety study, VAG-1748, being conducted in support of the registration of 10 mcg estradiol vaginal tablets in Europe. As of March 13, 2008, 335 postmenopausal women with uteri had been enrolled, 77 subjects had completed the 52-week study, 35 women had discontinued from the clinical trial, and 223 women were ongoing.

One death had been reported in Study VAG-1748 (Subject (b)(6), 77 years of age, treatment with 10 mcg estradiol vaginal tablets from (b)(6) until (b)(6), France). In (b)(6), Subject (b)(6) was diagnosed with cerebral metastasis of a primary unknown cancer. The subject died on (b)(6). An autopsy was not performed. The event was assessed as "unlikely related" to study medication by the investigator and the Sponsor. Eleven (11) additional subjects receiving 10 mcg estradiol vaginal tablets had SAEs. All of these additional SAEs were considered "unlikely related" to study medication by the investigator and the Sponsor. No events of endometrial hyperplasia or endometrial carcinoma have been reported in Study VAG-1748 as of the March 13, 2008 cut-off date.

Overall, the safety profile as presented in the integrated summary of safety is acceptable and is not sufficiently different from previously approved estrogen-only products (including the 25 mcg dose of Vagifem®) to raise any additional concerns or to not receive class labeling.

9. Advisory Committee

There were no controversial or difficult issues requiring input beyond that of the Agency reviewers from an Advisory Committee.

10. Pediatrics

The Sponsor requested a full waiver from the requirement to assess the safety and effectiveness of Vagifem® vaginal tablet in all relevant pediatric subpopulations in Accordance with 21 CFR 314.55(c)(2). The rationale for this request is that (b)(4) does not occur in pediatric patients and, therefore, use of this product prior to menarche is not indicated.
In an electronic mail communication dated May 15, 2008, the Pediatric and Maternal Health Division in the Office of New Drugs indicated that they concurred with the waiver.

11. Other Relevant Regulatory Issues

Two centers were recommended for Division of Scientific Investigation (DSI) audits. The sites were:

1. Investigator - Dr. Lonnie Clayton Harrell
   Clinical Site # 15
   Metrolina Medical Research
   1700 Abbey Place
   Suite 209
   Charlotte, NC 28209

2. Investigator - Dr. Robert Semo (replaced by Dr. William Koltun)
   Clinical Site # 30
   Medical Center for Clinical Research
   9040 Friars Road
   San Diego, CA 92108

DSI concluded that data generated from both sites for Study VAG-2195 appear acceptable for use in support of NDA 20-908/SE2-013.

The Medical Officer determined that the Sponsor disclosed financial arrangements with clinical investigators were consistent with the recommendation by the Agency in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators. No clinical investigator disclosed any "propriety interest in this product or a significant equity in the Sponsor as defined in 21 CFR 54.2(b)" and "no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

12. Labeling

Labeling negotiations were not pursued following review of the data for NDA 20-908/SE2-013

This reviewer notes the following consultative recommendations:

Division of Risk Management (DRISK):

- For consistency, we suggest adding the Patient Instructions for Use that appear in the original PPI to the PI. The PPI and PI should have consistent information.
- We suggest moving the instructions to the end of the PPI to be consistent with other patient labeling materials.

- We recommend including information on 10 mcg dosing and scheduling and on the number of doses in each carton, if this is different from the information provided for the 25 mcg dose.
- We added the following statement to the end of the section, "General information about the safe and effective use of Vagifem."
  "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."
  This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse events on Labeling for Human Drug Products in Federal Register Vol. 73, No.2, p.402-404, 1/3/2008).

Office of Surveillance and Epidemiology – Division of Adverse Event Analysis:
The review of data mining scores and the search of the AERS database for Vagifem did not identify and unlabeled adverse event terms for consideration as additions to the proposed labeling

Division of Medication Error Prevention and Analysis:
Based upon our assessment of the labels and labeling, DMEPA identified the following areas of needed improvement.

1. Replace all unit designations expressed as "µg" with "mcg" when expressed with a strength to be consistent with FDA's policy on excluding dangerous abbreviations and symbols from approved labels and labeling. FDA launched a campaign on June 14, 2006 warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g. trailing zeros).
2. Consider revising the carton labeling so that the (b)(4) (b)(4). In its current location, it may be more difficult to locate the (b)(4) because it is inconsistent from what consumers and healthcare practitioners are used to.
3. List the inactive ingredients on the carton labeling per 21 CFR 201.100 (b)(5).
4. The numbering in the patient labeling for the instructions is confusing in presentation and the figures are not coordinated with the text. Consider labeling figures alphabetically and reserve the numbers for the instruction steps.

13. Recommendations/ Risk Benefit Assessments

I concur with the Clinical/Statistical team that the results presented in SE2-013 do not support efficacy of the 10 mcg estradiol vaginal tablet for (b)(4) (b)(4). We recommend that NDA 20-908/SE2-013 not receive approval. No additional risk:benefit assessment is requested.

APPENDIX

Table X – Listing of Subjects Utilized in September 24, 2008 Interim FDA Analysis of Dyspareunia – mITT-1 Population (LOCF)

Obs	PT	trt	QSTESTCD	Bas_pain	pain2	pain4	pain8	pain12	cpain
1	(b)(6)	VLD	URO5	2	1	2	2	2	0
2		Placebo	URO5	2	1	1	1	1	1
3		Placebo	URO5	2	1	1	1	2	0
4		Placebo	URO5	3	2	2	1	0	3
5		VLD	URO5	2	.	0	0	1	1
6		Placebo	URO5	2	2	2	2	2	0
7		VLD	URO5	2	0	0	0	0	2
8		Placebo	URO5	2	2	2	2	2	0
9		VLD	URO5	2	1	0	0	0	2
10		VLD	URO5	2	1	0	1	1	1
11		VLD	URO5	2	1	0	0	0	2
12		VLD	URO5	2	2	2	1	1	1
13		Placebo	URO5	3	3	3	3	3	0
14		VLD	URO5	3	3	2	3	3	0
15		VLD	URO5	2	2	2	1	1	1
16		Placebo	URO5	2	1	0	1	1	1
17		VLD	URO5	3	3	1	1	0	3
18		VLD	URO5	3	3	2	2	2	1
19		VLD	URO5	3	.	.	.	0	3
20		Placebo	URO5	3	2	2	1	2	1
21		VLD	URO5	2	1	2	1	2	0
22		VLD	URO5	3	3	2	1	1	2
23		Placebo	URO5	3	3	3	3	3	0
24		Placebo	URO5	2	2	2	2	2	0
25		VLD	URO5	3	3	0	0	0	3
26		Placebo	URO5	3	3	3	1	1	2
27		VLD	URO5	2	3	0	2	1	1
28		Placebo	URO5	3	2	1	1	1	2
29		Placebo	URO5	3	.	3	3	3	0
30		VLD	URO5	3	3	3	3	3	0
31		VLD	URO5	3	3	2	2	2	1
32		VLD	URO5	3	.	3	3	3	0
33		VLD	URO5	3	1	1	0	0	3
34		VLD	URO5	2	0	0	0	0	2
35		Placebo	URO5	2	3	3	3	2	0
36		Placebo	URO5	3	.	1	2	1	2
37		VLD	URO5	3	3	3	2	2	1
38		Placebo	URO5	3	1	1	1	1	2
39		Placebo	URO5	3	.	1	1	2	1
40		VLD	URO5	2	.	2	3	2	0
41		Placebo	URO5	2	1	0	1	1	1
42		VLD	URO5	2	0	1	1	0	2
43		VLD	URO5	3	3	3	2	1	2
44		Placebo	URO5	3	3	3	3	3	0
45		VLD	URO5	3	3	1	2	2	1
46		Placebo	URO5	3	1	1	1	1	2
47		VLD	URO5	3	3	3	2	1	2
48		VLD	URO5	2	2	2	1	1	1
49		Placebo	URO5	2	1	1	1	1	1
50		VLD	URO5	3	3	3	1	1	2

Obs	PT	trt	QSTESTCD	Bas_pain	pain2	pain4	pain8	pain12	cpain
	(b)(6)								
51		VLD	UR05	3	3	3	2	2	1
52		Placebo	UR05	2	2	2	2	2	0
53		VLD	UR05	3	0	0	0	1	2
54		VLD	UR05	3	3	3	3	3	0
55		VLD	UR05	2	.	1	2	1	1
56		VLD	UR05	2	2	1	1	1	1
57		VLD	UR05	3	.	2	2	2	1
58		VLD	UR05	3	0	0	0	0	3
59		VLD	UR05	3	3	2	0	1	2
60		Placebo	UR05	2	1	1	1	1	1
61		VLD	UR05	2	1	1	1	1	1
62		VLD	UR05	3	3	3	2	2	1
63		Placebo	UR05	2	2	2	2	2	0
64		Placebo	UR05	3	3	3	3	3	0
65		Placebo	UR05	2	1	1	1	1	1
66		VLD	UR05	2	3	1	0	0	2
67		VLD	UR05	3	2	2	3	2	1
68		VLD	UR05	3	3	2	1	1	2
69		VLD	UR05	3	3	1	2	1	2
70		Placebo	UR05	2	.	1	1	1	1
71		Placebo	UR05	2	1	1	1	0	2
72		VLD	UR05	3	2	3	3	1	2
73		VLD	UR05	3	3	2	3	3	0
74		Placebo	UR05	3	1	2	1	1	2
75		VLD	UR05	3	2	2	3	2	1
76		Placebo	UR05	3	2	2	2	2	1
77		VLD	UR05	3	2	1	0	0	3
78		VLD	UR05	3	2	1	1	1	2
79		VLD	UR05	2	0	0	0	0	2
80		VLD	UR05	3	3	3	3	3	0
81		VLD	UR05	2	2	2	3	2	0
82		Placebo	UR05	2	2	1	1	0	2
83		Placebo	UR05	3	2	1	2	2	1
84		VLD	UR05	3	3	3	3	3	0
85		Placebo	UR05	3	1	1	3	3	0
86		Placebo	UR05	3	2	3	3	3	0
87		VLD	UR05	2	1	1	0	0	2
88		VLD	UR05	3	3	3	3	3	0
89		Placebo	UR05	3	.	2	2	2	1
90		VLD	UR05	2	0	0	0	0	2
91		Placebo	UR05	3	3	3	3	3	0
92		VLD	UR05	3	.	1	1	2	1
93		VLD	UR05	3	1	2	1	1	2
94		VLD	UR05	2	2	1	1	1	1
95		Placebo	UR05	3	3	3	2	1	2
96		Placebo	UR05	3	.	1	1	1	2
97		VLD	UR05	2	1	1	1	1	1
98		VLD	UR05	3	3	3	1	0	3
99		Placebo	UR05	3	.	.	1	1	2
100		VLD	UR05	3	2	3	2	3	0

Obs	PT	trt	QSTESTCD	Bas_pain	pain2	pain4	pain8	pain12	cpain
	(b)(6)								
101		Placebo	URO5	2	.	.	2	2	0
102		VLD	URO5	3	3	3	3	3	0
103		VLD	URO5	3	3	3	3	2	1
104		VLD	URO5	2	1	1	2	2	0
105		VLD	URO5	3	2	2	2	2	1
106		VLD	URO5	2	1	2	1	1	1
107		VLD	URO5	3	.	3	2	2	1
108		VLD	URO5	2	3	2	2	1	1
109		Placebo	URO5	3	3	3	2	3	0
110		VLD	URO5	3	.	1	1	2	1
111		Placebo	URO5	3	3	2	2	1	2
112		VLD	URO5	3	1	1	0	0	3
113		VLD	URO5	3	3	1	2	2	1
114		VLD	URO5	3	3	2	2	2	1
115		VLD	URO5	2	1	2	1	1	1

Table Y - Listing of 122 Subjects Submitted by the Sponsor as Meeting Baseline Criteria for Superficial cells, pH and Most Bothersome Moderate to Severe Symptom of Dyspareunia. Includes Severity Scoring at Baseline, 2. 4, 8 and 12 weeks – September 16, 2008 submission.

Color coded subjects indicate those not included in FDA or Sponsor analyses or with questions by the Sponsor on LOCF.

Appears this way on original

Obs	pt	trt	qstestcd	Bas_pain	pain2	pain4	pain8	pain12	pain12_locf
1	(b)(6)	VLD	UROS	2	1	2	1		1
2		Placebo	UROS	2	1	1			1
3		Placebo	UROS	2	1	1	1	2	2
4		Placebo	UROS	3	2	2	1	0	0
5		VLD	UROS	2	NA	0	0	1	1
6		Placebo	UROS	2	2	2	2	NA	NA
7		VLD	UROS	2	0	0	0	NA	NA
8		Placebo	UROS	2	2	2	2	NA	NA
9		Placebo	UROS	3	3				3
10		VLD	UROS	2	1	0	0	0	0
11		VLD	UROS	2	1	0	1	1	1
12		VLD	UROS	2	1	0	0	0	0
13		VLD	UROS	2	2	2	1	1	1
14		Placebo	UROS	3	3	3	3	3	3
15		VLD	UROS	3	3	2	3	3	3
16		VLD	UROS	2	2	2	1	1	1
17		Placebo	UROS	2	1	0	1	1	1
18		VLD	UROS	3	3	1	1	0	0
19		VLD	UROS	3	3	2	NA	NA	NA
20		VLD	UROS	3	NA	NA	NA	0	0
21		Placebo	UROS	3	2	2	1	2	2
22		VLD	UROS	2	1	2	1	2	2
23		VLD	UROS	3	3	2	1	1	1
24		Placebo	UROS	3	3	3			3
25		Placebo	UROS	2	2	NA	2	2	2
26		VLD	UROS	3	3	0	0	0	0
27		Placebo	UROS	3	3	3	1	1	1
28		VLD	UROS	2	3	0	2	1	1
29		Placebo	UROS	3	2	1	1	1	1
30		Placebo	UROS	3	NA	3	NA	NA	NA
31		VLD	UROS	3	3	3	3	NA	NA
32		VLD	UROS	3	3	2	2	2	2
33		VLD	UROS	3	NA	3	3	3	3
34		VLD	UROS	3	1	1	0	0	0
35		VLD	UROS	2	0	0	0	0	0
36		Placebo	UROS	2	3	3	3	2	2
37		Placebo	UROS	3	NA	1	2	1	1
38		VLD	UROS	3	3	3	2	NA	NA
39		Placebo	UROS	3	1	1	1	1	1
40		Placebo	UROS	3	NA	1	1	2	2
41		VLD	UROS	2	NA	2	3	2	2
42		Placebo	UROS	2	1	0	1	1	1
43		VLD	UROS	2	0	1	1	0	0
44		VLD	UROS	3	3	NA	2	1	1
45		Placebo	UROS	3	3	3	NA	NA	NA
46		VLD	UROS	3	3	1	2	2	2
47		Placebo	UROS	3	1	1	1	1	1
48		VLD	UROS	3	3	3	2	1	1
49		VLD	UROS	2	2	NA	1	1	1
50		Placebo	UROS	2	1	1	1	1	1
51		VLD	UROS	3	3	3	1	1	1
52		VLD	UROS	3	3	3	2	2	2
53		VLD	UROS	3	2				2

Obs	pt	trt	qstestcd	Bas_pain	pain2	pain4	pain8	pain12	pain12_locf
54	(b)(6)	Placebo	URO5	2	2	2	2	2	2
55		VLD	URO5	3	0	0	0	1	1
56		VLD	URO5	3	3	3	3	3	3
57		VLD	URO5	2		1	2	1	1
58		VLD	URO5	2	2	1	1	1	1
59		VLD	URO5	3	NA	2	2	NA	NA
60		VLD	URO5	3	0	NA	0	NA	NA
61		VLD	URO5	3	3	2	0	1	1
62		Placebo	URO5	2	1	1	1	1	1
63		Placebo	URO5	3	NA	NA	3		3
64		VLD	URO5	2	1	1	1	1	1
65		VLD	URO5	3	3	3	2	2	2
66		Placebo	URO5	2	2	NA	2	NA	NA
67		Placebo	URO5	3	3	3	2		2
68		Placebo	URO5	2	1	1	3		3
69		VLD	URO5	2	3	1	0	NA	NA
70		VLD	URO5	3	2	NA	3	2	2
71		VLD	URO5	3	3	2	1	1	1
72		VLD	URO5	3	3	1	2	1	1
73		Placebo	URO5	2	NA	1	1	1	1
74		Placebo	URO5	2	1	1	1	0	0
75		VLD	URO5	3	2	3	NA	1	1
76		VLD	URO5	3	3	2	3	3	3
77		Placebo	URO5	3	1	2	1	1	1
78		VLD	URO5	3	3				3
79		VLD	URO5	3	2	2	3	2	2
80		Placebo	URO5	3	2	2	2	2	2
81		VLD	URO5	3	2	1	0	0	0
82		VLD	URO5	3	2	1	1	1	1
83		VLD	URO5	2	0	0	0	0	0
84		VLD	URO5	3	3	3	3	3	3
85		VLD	URO5	2	2	2	3	2	2
86		Placebo	URO5	2	2	1	1	0	0
87		Placebo	URO5	3	2	1	2	2	2
88		VLD	URO5	3	3	3	3	NA	NA
89		Placebo	URO5	3	NA	3			3
90		VLD	URO5	2	2				2
91		Placebo	URO5	3	1	NA	3	3	3
92		Placebo	URO5	3	2	3	NA	3	3
93		VLD	URO5	2	1	1	0	0	0
94		VLD	URO5	3	3	NA	NA	NA	NA
95		Placebo	URO5	3	NA	2	2	NA	NA
96		VLD	URO5	2	0	0	0	0	0
97		Placebo	URO5	3	3	3	3	3	3
98		VLD	URO5	3	NA	1	1	2	2
99		VLD	URO5	3	1	2	1	1	1
100		VLD	URO5	2	2	1	1	1	1
101		Placebo	URO5	3	3	3	2	1	1
102		Placebo	URO5	3	NA	1	1	1	1
103		VLD	URO5	2	1	1	1	1	1
104		VLD	URO5	3	3	NA	1	0	0
105		Placebo	URO5	3	NA	NA	1	1	1
106		VLD	URO5	3	2	3	2	3	3

Obs	pt	trt	qstestcd	Bas_pain	pain2	pain4	pain8	pain12	pain12_locf
107	(b)(6)	Placebo	URO5	2	NA	NA	2	2	2
108		VLD	URO5	3	3	3	3	3	3
109		VLD	URO5	3	3	NA	NA	2	2
110		VLD	URO5	2	1	NA	2	NA	NA
111		VLD	URO5	3	2	2	2	2	2
112		VLD	URO5	2	1	2	1	1	1
113		VLD	URO5	3	NA	3	2	2	2
114		VLD	URO5	2	3	2	2	1	1
115		Placebo	URO5	3	3	3	2	3	3
116		Placebo	URO5	3	NA	NA	2		2
117		VLD	URO5	3	NA	1	1	2	2
118		Placebo	URO5	3	3	2	2	1	1
119		VLD	URO5	3	1	1	0	0	0
120		VLD	URO5	3	3	1	2	2	2
121		VLD	URO5	3	3	2	2	2	2
122		VLD	URO5	2	1	2	1	1	1

Four (4) pages have been redacted as (b)(4), CCI/TS, immediately following this page.

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/s/

Shelley Slaughter
10/10/2008 06:35:50 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

CLINICAL REVIEW(S)

CLINICAL REVIEW OF CLASS 2 RE-SUBMISSION

Application Type	Supplemental NDA Complete Response (CR)
Submission Number	20-908
Submission Code	SE1-013
CR Letter Date	May 26, 2009
PDUFA Goal Date	November 26, 2009
Reviewer Name	Theresa H. van der Vlugt, MD
Review Completion Date	September 16, 2009
Review Revised Date	November 10, 2009
Established Name	Estradiol vaginal tablet
Trade Name	Vagifem®
Therapeutic Class	Estrogen
Applicant	Novo Nordisk, Inc.
Priority Designation	3S
Formulation	Vaginal tablet
Dosing Regimen	One 10 microgram (mcg) estradiol vaginal tablet inserted intravaginally daily for two weeks, then one tablet inserted twice weekly
Proposed Indication	(b)(4)
Intended Population	Postmenopausal women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends the approval of the 10 mcg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions for the treatment of atrophic vaginitis due to menopause based on the data presented in the Complete Response re-submission for Supplemental NDA 20-908/SE1-013. The re-submission re-analysis of the intent-to-treat (ITT) study population (defined by the Applicant as all randomized subjects who take at least one dose of trial medication and have a baseline and at least one post-baseline efficacy assessment) using last observation carried forward (LOCF) provides sufficient evidence to conclude that the 10 mcg estradiol vaginal tablet demonstrates a statistically significant mean change between baseline and week 12, compared to the placebo vaginal tablet, in a composite of the subject's self-assessed most bothersome symptoms of atrophic vaginitis at baseline ($p=0.002$). A statistically significant mean change in vaginal superficial and parabasal cells and vaginal pH score between baseline and week 12 (LOCF) for the 10 mcg estradiol vaginal tablet, compared to the placebo vaginal tablet, was also demonstrated ($p<0.001$ for both endpoints). Vagifem® (estradiol vaginal tablets) 25 mcg was approved on March 26, 1999 for the treatment of atrophic vaginitis based on similar considerations and is currently marketed in the U.S.

The safety of the 10 mcg estradiol vaginal tablet was not a concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved to treat moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 clinical study is proposed.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Vagifem® (estradiol vaginal tablets) 25 mcg was approved in the U.S. on March 26, 1999 for the treatment of atrophic vaginitis, based on the change in a composite score for the three symptoms of dryness, soreness, and irritation as measured at week 12, and became commercially available in year 2000.

Supplemental NDA 20-908/SE1-013 was originally submitted on December 7, 2007 for the 10 mcg estradiol vaginal tablet for the proposed indication of "(b)(4) (b)(4)." The primary source of safety and efficacy data submitted was single, 52-week Phase 3a Study VAG-2195. In Study VAG-2195, 309 healthy postmenopausal women were randomized to receive:

- Estradiol vaginal tablet, 10 mcg (one vaginal tablet inserted daily for 2 weeks and then one vaginal tablet inserted twice-weekly thereafter)
- Placebo vaginal tablet (one vaginal tablet inserted daily for 2 weeks and then one vaginal tablet inserted twice-weekly thereafter)

The primary objective of Study VAG-2195 was "to evaluate the efficacy of Vagifem 10 µg compared to placebo as assessed by the clinical symptoms and the objective parameters." The co-primary efficacy endpoints were the mean change from baseline to week 12 in the:

1) "Vaginal Maturation Index (parabasal and superficial epithelial cells),
2) Vaginal pH, and
3) The moderate to severe symptom that was identified by the patient as being most bothersome to her."

The secondary objective of Study VAG-2195 was to "evaluate the endometrial safety from endometrial biopsies taken at the beginning and at the end of study treatment (52 weeks)."

Two sources of safety data were submitted in original sNDA 20-908/SE1-013 on December 7, 2007: Phase 3a Study VAG-2195 and Phase 1 bioavailability Study VAG-1850. A total of 308 treated subjects are represented in 52-week Study VAG-2195: 205 subjects were treated with 10 mcg estradiol vaginal tablets and 103 subjects were treated with placebo vaginal tablets. A total of 57 subjects were treated in Study VAG-1850: 29 subjects received 10 mcg estradiol vaginal tablets and 28 subjects received Vagifem® 25 mcg.

One additional source of safety data was submitted in the Class 2 Re-Submission on May 26, 2009. A total of 336 treated subjects are represented in non-IND, open-label, 52-week Study VAG-1748. All of the subjects in Study VAG-1748 received 10 mcg estradiol vaginal tablets.

1.3.2 Efficacy

See the Medical Officer's Primary Review dated October 6, 2008 and the Statistical Primary Review dated October 8, 2008 for a detailed description of the efficacy data submitted, either in the original submission or upon request of the Division of Reproductive and Urologic Products (DRUP), and reviewed during the first review cycle. See also the Medical Team Leader's Primary Review dated October 7, 2008 and the Division Director's Primary Review dated October 14, 2008.

The Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (referred to elsewhere in this document as the Agency's 2003 draft clinical evaluation guidance document) recommends that effectiveness be demonstrated in three co-primary endpoints for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause (VVA):

- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells).
- Mean change from baseline to week 12 in vaginal pH.
- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her.

Phase 3a Study VAG-2195 was the pivotal safety and efficacy study submitted in the original December 7, 2007 submission. Phase 3a Study VAG-2195 investigated the mean change between baseline and week 12 of six vulvar and vaginal atrophy symptoms (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia and vaginal bleeding associated with sexual activity). The results from the original ANCOVA on rank analyses for the first 12 weeks of 52-week Phase 3a Study VAG-2195, for the Division's defined mITT-1 study population (representing a subset of the mITT population who identified at baseline a moderate to severe most bothersome vaginal symptom and had a vaginal pH of ≥ 5.0 and a vaginal cytology with $\leq 5\%$ superficial epithelial cells) and mITT-2 study population (representing subjects who identified at baseline a moderate to severe most bothersome symptom of VVA, without consideration of their baseline vaginal pH value or the baseline proportion of vaginal superficial epithelial cells on a vaginal smear) did not demonstrate statistical effectiveness (when adjusted for multiplicity) for the 10 mcg estradiol vaginal tablet versus the placebo vaginal tablet for any individual moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. A statistically significant difference versus placebo for the 10 mcg estradiol vaginal tablet for the remaining two recommended co-primary endpoints: (1) mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells), and (2) mean change from baseline to week 12 in vaginal pH was demonstrated ($p<0.001$ for both of these endpoints). However, based on the 2003 draft clinical evaluation guidance document, all three co-primary endpoints must demonstrate a statistically significant difference versus placebo (b)(4) Thus, the original December 7, 2007 data submitted for Phase 3a Study VAG-2195 did not meet efficacy for the

(b)(4)
as defined by the Agency's 2003 draft clinical evaluation guidance document.

Novo Nordisk Inc. received the Division's Complete Response letter on October 15, 2008 indicating "we cannot approve this application in its present form".

Novo Nordisk Inc. was granted a Type A meeting which was held on March 20, 2009. DRUP's official minutes of the meeting offered the following post-meeting comments and recommendations:

1. "Based on the discussion and clarification provided by Novo Nordisk, the Division acknowledges that the Applicant may not have fully understood the intent of the draft Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom" prior to the Division's letter of September, 2007."
2. "The Division believes that the clinical deficiency regarding the efficacy of Vagifem (estradiol vaginal tablets) 10 µg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified primary analysis. The Division, however, will need to confirm that the Applicant's composite re-analysis for the most bothersome symptom supports a finding that treatment with Vagifem 10 µg is statistically superior to treatment with placebo."

Novo Nordisk Inc. was requested to provide the following documents in the sNDA 20-908/SE1-013 re-submission:

- background information and justification for the design and analysis of Study VAG-2195;
- the "White Paper" presented by (b)(4) at the March 20, 2009 Type A meeting;
- data file(s) to support the protocol-defined primary analysis for the most bothersome symptom and case report forms (CRFs) to confirm the baseline and Week 12 (or last observation carried forward [LOCF] values in the data file(s);
- the final Report (or alternatively, an abbreviated interim final Report) for completed Study VAG-1748 (endometrial safety study); and
- proposed product labeling and a safety update as described in the Complete Response letter of October 15, 2008.

On May 26, 2009, Novo Nordisk Inc. submitted a Class 2 Re-Submission for the 10 mcg estradiol vaginal tablet. The re-submission contained the requested information including a re-analysis of a composite of all most bothersome VVA symptoms, and the final report of a 12-month non-IND safety study (Study VAG-1748).

The original protocol submitted under IND (b)(4) for Study VAG-2195 defined the intent-to treat (ITT) population as "all randomized subjects who take at least one dose of trial medication and have baseline and one post-baseline assessment for any efficacy parameter (urogenital symptoms, vaginal pH, and Vaginal Maturation Index and Score)". The original "protocol-specified primary analysis" stated, "symptoms associated with atrophic vaginitis (dryness, soreness, irritation, dyspareunia, and vaginal discharge) will be graded none, mild,

moderate, and severe, and scored as 0, 1, 2, and 3, respectively. An average score of dryness, soreness, and irritation will be calculated. An analysis of covariance (ANCOVA) will be used for the between group comparison with treatment and center included as fixed effects and corresponding baseline value as a covariate. The same ANCOVA model will be used to analyze MV and pH." Amendment 1 to Study VAG-2195, received on March 11, 2005, revised the symptoms associated with atrophic vaginitis to include vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, pain associated with sexual activity (dyspareunia) and bleeding associated with sexual activity. Amendment 2 to Study VAG-2195, received on February 24, 2006, reduced the total planned study population from 600 subjects (400 treated with 10 mcg estradiol vaginal tablet and 200 treated with placebo vaginal tablet) to 300 subjects (200 treated with 10 mcg estradiol vaginal tablet and 100 treated with placebo vaginal tablet) due to slow enrollment.

Following the Type A meeting held on March 20, 2009, DRUP agreed to consider a re-analysis of a composite of all most bothersome symptoms based on the protocol-specified primary analysis submitted under IND (b)(4) on (b)(4) The mean change in a composite score of three symptoms (vaginal dryness, soreness, and irritation) between baseline and week 12 supported the approval of Vagifem® 25 mcg for the treatment of atrophic vaginitis in year 1999.

The Applicant's re-analysis for the composite score of all most bothersome symptoms for the protocol-specified ITT study population in Phase 3a Study VAG-2195, submitted May 26, 2009, demonstrates a statistically significant difference ($p=0.002$) in the mean change from baseline for the 10 mcg estradiol vaginal tablet compared to the placebo vaginal tablet at week 12 (LOCF) (see Table 4). The Agency's recommended co-primary endpoints of mean change in vaginal superficial and parabasal cells as well as the mean change in vaginal pH were also met in the primary Phase 3a Study VAG-2195 ($p<0.001$ for both of these endpoints) (see Tables 2 and 3).

1.3.3 Safety

The safety data presented in the December 7, 2007 submission and the May 26, 2009 Class 2 Re-Submission demonstrates an acceptable overall safety profile of the 10 mcg estradiol vaginal tablet, administered intravaginally daily for two weeks and then twice-weekly thereafter.

See the Medical Officer's Primary Review dated October 6, 2008 for a detailed description of the safety data submitted, either in the original submission or upon request of DRUP, and reviewed during the first review cycle.

The Agency was advised at the March 20, 2009 Type A meeting that the non-IND, open-label, 52-week, endometrial safety clinical trial (Study VAG-1748) conducted in Europe (Czech Republic, Denmark, Finland, France, Hungary, and Sweden) was now completed and closed for database review. Study VAG-1748 was conducted to meet the safety requirements of the European Medicines Agency (EMEA) of 12 months of endometrial safety data on at least 300 completed patients.

On May 26, 2009, the Applicant submitted a safety update and the final report for Study VAG-1748 as parts of the re-submission. On May 28, 2009, Novo Nordisk Inc. also submitted an international Periodic Safety Update Report (PSUR) for Vagifem® (estradiol vaginal tablets) 25 mcg.

An Integrated Summary of Safety (ISS), submitted on July 2, 2009, incorporated primary Phase 3a Study VAG-2195 and completed non-IND, 12-month Phase 3 Study VAG-1748. The July 2, 2009 submission includes a pooled analysis of endometrial biopsy results for the two studies.

No deaths occurred during the conduct of 52-week Study VAG-2195 or 12-week Study VAG-1850. One death occurred during the conduct of 52-week Study VAG-1748. Subject (b)(6) a 77 year old postmenopausal woman treated in France received 10 mcg estradiol vaginal tablets between (b)(6) and (b)(6) (approximately 9 months of treatment) and died on (b)(6). She was diagnosed with cerebral metastasis of a primary unknown cancer. An autopsy was not performed. Screening procedures for Subject (b)(6) were reported as negative for breast, endometrium, and cervix. The investigator and Novo Nordisk Inc. assessed the relationship causality of the event as unlikely related given the "advanced stage cancer of unknown primary location after only 9 months of treatment".

Seven (7) subjects experienced serious adverse events (SAEs) in Study VAG-2195 (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [2.4%, 5 of 205 treated subjects] and 2 subjects in the placebo vaginal tablet treatment group [2%, 2 of 103 treated subjects]). Fourteen (14) subjects experienced SAEs in Study VAG-1748 (4.2%, 14 of 336 subjects treated with 10 mcg estradiol vaginal tablets). No subject in Study VAG-1850 experienced a SAE.

The SAEs reported in Study VAG-2195 and Study VAG-1748 do not raise safety concerns.

1.3.4 Dosing Regimen and Administration

Vagifem® 25 mcg (estradiol vaginal tablets), administered intravaginally daily for 2 weeks then twice-weekly thereafter, is approved for the treatment of atrophic vaginitis, and is only intended for intravaginal use in postmenopausal women.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

In vitro and *in vivo* studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin may reduce

plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling

1.3.6 Special Populations

Estradiol vaginal tablet (10 mcg) is only intended for use in postmenopausal women. In Phase 3a Study VAG-2195 and Phase 3 Study VAG-1748, conducted for the 10 mcg estradiol vaginal tablet dosing regimen, there was an insufficient numbers of geriatric subjects to determine if those over 65 years of age differ from younger subjects in their response to 10 mcg estradiol vaginal tablets.

Estradiol vaginal tablet (10 mcg) was not studied in women with liver disease or renal impairment. Estradiol vaginal tablet (10 mcg) should not be used in pregnant women.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vagifem® (estradiol vaginal tablets) 25 mcg was approved in the U.S. on March 26, 1999 for the treatment of atrophic vaginitis and became commercially available in year 2000. Data from two 12-week clinical trials (VAG/PD/9/USA [placebo-controlled] and VAG/PD/5/CAN [active-controlled]), conducted during the development program, supported the approval of Vagifem® 25 mcg.

In the original submission of Supplemental NDA 20-908/SE1-013, the results of two completed clinical trials were included in support of drug approval: 1) Phase 3a Study VAG-2195 assessed safety and effectiveness of the 10 mcg estradiol vaginal tablet in postmenopausal women with signs and symptoms of atrophic vaginitis; 2) Phase 1 Study VAG-1850 was an open label, single center, multiple dose, 12-week clinical trial conducted to evaluate the systemic estradiol absorption of the 10 mcg estradiol vaginal tablet. Study VAG-1850 also provided supporting evidence of safety.

On October 15, 2008, Novo Nordisk received the Division's Complete Response letter indicating "we cannot approve this application in its present form." The reasons for the Complete Response action and recommendations to address issues indicated the following:

Deficiency

"Adequate evidence has not been provided to support the effectiveness of Vagifem (estradiol vaginal tablets) 10 µg for the (b)(4) (b)(4). In the analysis of the modified intent-to-treat (m-ITT) population (representing subjects who identified at baseline a moderate to severe most bothersome symptom of VVA, without consideration of their baseline vaginal pH and vaginal cytology), subjects treated with Vagifem (estradiol vaginal tablets) 10 µg did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual moderate to severe symptom of VVA. In the analysis of the m-ITT population as identified in the Agency's advice letter of November 15, 2007 (representing those subjects who identified at baseline a moderate to severe most bothersome symptom and who had a vaginal pH of 5.0 or greater and a vaginal cytology of 5% or less superficial cells), subjects treated with Vagifem (estradiol vaginal tablets) 10 µg also did not demonstrate a statistically significant greater reduction in the severity of at least one individual moderate to severe symptom of VVA, based on an appropriate non-parametric analysis and adjustment for multiplicity."

Resolution of Deficiency

"To address the above deficiency, conduct and submit the results of an adequate and placebo-controlled trial to demonstrate the efficacy of Vagifem (estradiol vaginal tablets) 10 µg for the [redacted] (b)(4). The trial should enroll subjects with a self-identified moderate to severe most bothersome symptom of VVA due to menopause, a vaginal pH of greater than 5.0, and 5% or fewer superficial cells on a smear from the vaginal wall. The trial should be powered to demonstrate the following at Week 12:

1. A statistically significant improvement over placebo for at least one individual moderate to severe symptom of VVA self-identified by subjects as most bothersome at baseline.
2. A decrease in vaginal pH, and
3. An increase in superficial cells and a decrease in parabasal cells on a smear from the vaginal wall.

If you do not pre-specify the individual moderate to severe most bothersome symptom of VVA that will be investigated, the statistical analysis plan should address the issue of multiplicity. Other details of the trial can be discussed with the Division prior to or at the time of submission of a new protocol."

In addition to the clinical and statistical issues mentioned above, the October 15, 2008 Complete Response letter outlined the requirements for a safety update from all nonclinical and clinical studies/trials of estradiol vaginal tablets regardless of indication, dosage form, or dose level.

Novo Nordisk Inc. requested a Type A meeting with the Agency which was held on March 20, 2009. Per the pre-meeting information provided by Novo Nordisk Inc. on January 9, 2009, the purpose of the requested meeting was:

- "To discuss with the Division efficacy data for the subjective parameter "most bothersome symptom" (MBS), which is a co-primary endpoint as specified in the 2003 FDA Draft Guidance and provided in the original registration trial VAG-2195, submitted in S-013 on December 7, 2008 for Vagifem 10 mcg tablets.
- To resolve with the Division appropriate statistical methodologies for FDA-requested subgroups and post-hoc analyses.
- To clarify with the Division the interpretation of the modified intent-to-treat (mITT-2) population in assessing Vagifem 10 µg."

"This meeting will facilitate sharing information between the Division and the Sponsor. Its purpose is to seek resolution of the Division's Complete Response Letter of October 15, 2008 or to serve as discussion prior to starting formal dispute appeal procedures. (21 CFR 214.102 and 314.103)"

In the Agency's official minutes of the March 20, 2009 meeting provided to the Applicant on April 17, 2009, DRUP offered the following post-meeting comments and recommendations:

1. "Based on the discussion and clarification provided by Novo Nordisk, the Division acknowledges that the Applicant may not have fully understood the intent of the draft Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom" prior to the Division's letter of September, 2007."
2. "The Division believes that the clinical deficiency regarding the efficacy of Vagifem (estradiol vaginal tablets) 10 µg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified primary analysis. The Division, however, will need to confirm that the Applicant's composite re-analysis for the most bothersome symptom supports a finding that treatment with Vagifem 10 µg is statistically superior to treatment with placebo."

Novo Nordisk Inc. was requested to provide the following documents in the sNDA 20-908/SE1-013 re-submission:

- background information and justification for the design and analysis of Study VAG-2195;
- the "White Paper" presented by (b)(4) at the March 20, 2009 Type A meeting;
- data file(s) to support the protocol-defined primary analysis for the most bothersome symptom and case report forms (CRFs) to confirm the baseline and Week 12 (or last observation carried forward [LOCF] values in the data file(s);
- the final Report (or alternatively, an abbreviated interim final Report) for completed Study VAG-1748 (endometrial safety study); and
- proposed product labeling and a safety update as described in the Complete Response letter of October 15, 2008.

2.2 Currently Available Treatment for Indications

See the Medical Officer's Primary Review of sNDA 20-908/SE1-013, dated October 6, 2008, for a detailed description of estrogen-alone and estrogen plus progestin drug products currently approved for the treatment of vulvar and vaginal atrophy (VVA) due to menopause and/or the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause.

The numerous currently approved estrogen-alone or estrogen plus progestin drug products for VVA and/or VMS indications offer a range of dosage forms (oral tablets, transdermal systems, topical and vaginal products) and dosage strengths.

2.3 Availability of Proposed Active Ingredient in the United States

See the Medical Officer's Primary Review of NDA 20-908/SE1-013, dated October 6, 2008, for a detailed description of all estradiol products currently approved and marketed in the U.S. for the treatment of VVA.

2.4 Important Issues With Pharmacologically Related Products

After an average follow-up of 5.2 years, the conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) substudy of the Women's Health Initiative (WHI) study was stopped early (year 2002) because the increased risk of breast cancer and cardiovascular events exceeded the pre-specified limits in the "Global Index". Centrally adjudicated data, after an average follow-up of 5.6 years, reported an increased risk of invasive breast cancer (relative risk [RR] of 1.24 with a 95% nominal confidence interval [nCI], 1.01-1.54), increased risk of all stroke (RR 1.31, 95% CI, 1.02-1.68) and ischemic stroke (RR 1.44, 95% CI, 1.09-1.90), increased risk of coronary heart disease (RR 1.23, 95% CI, 0.99-1.53), increased risk of probable dementia (RR 2.05, 95 percent CI, 1.21-3.48), and a decreased risk of hip fracture (RR 0.67, 95 percent CI, 0.47-0.96).

The risk and benefit information available in the WHI estrogen plus progestin substudy in year 2002 prompted changes in labeling for estrogen class drug products including, but not limited to, the addition of a boxed warning to all estrogen plus progestin product labels and the expansion of the existing boxed warning in all estrogen-alone product labels to include the increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis reported in the estrogen plus progestin WHI substudy. In addition, boxed warning information states that "---in the absence of comparable data, these risks should be assumed to be similar" for "other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestin", and that "---estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women."

After an average follow-up of 6.8 years, the WHI estrogen-alone substudy was also stopped early (year 2004) because the use of CE-alone increased the risk of stroke (RR 1.39, 95% nCI, 1.10-1.77) (conjugated estrogens-alone versus placebo), and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints. Centrally adjudicated results reported for the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, reported an increased risk for all stroke (RR 1.33, 95% nCI, 1.05-1.68) (CE versus placebo) and ischemic stroke (RR 1.55, 95% nCI, 1.19-2.01). No effect on coronary heart disease, after an average follow-up of 7.1 years, was reported (RR 0.95, 95% nCI, 0.78-1.16). Other findings in the CE-alone substudy, based on an average follow-up of 7.1 years, included a decreased risk of hip fracture (RR 0.65, 95% nCI, 0.45-0.94), a decreased risk of invasive breast cancer (RR 0.80, 95% nCI, 0.62-1.04), and an increased risk for probable dementia (RR 1.49, 95% CI, 0.83-2.66).

The risk and benefit information available in the WHI estrogen-alone substudy in year 2004 prompted changes in labeling for estrogen class drug products including, but not limited to, the expansion of the boxed warning to include the reported increased risk of stroke in the WHI estrogen-alone substudy. In years 2006 and 2007, additional changes were made in labeling for estrogen class drug products based on centrally adjudicated results for the WHI estrogen-alone substudy.

Risk information available in the WHI Memory Study (WHIMS) in years 2003 and 2004 prompted additional changes in labeling for estrogen class drug products to include the reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older. WHIMS findings for both the estrogen-alone ancillary study and the estrogen plus progestin ancillary study were added to the boxed warning, and the clinical studies, warnings and precautions sections of estrogen class labeling.

2.5 Presubmission Regulatory Activity

See the Medical Officer's Primary Review of sNDA 20-908/SE1-013, dated October 6, 2008, for a detailed description of regulatory activity prior to the original submission of sNDA 20-908/SE1-013 and during the first review cycle.

In the Medical Officer's review of the original submission of sNDA 20-908/SE1-013 dated October 6, 2008, this reviewer did not recommend approval of the 10 mcg estradiol vaginal tablet for the "(b)(4) (b)(4)". In the original sNDA application, the Agency analyzed the data presented for single Phase 3a Study VAG-2195 using a non-parametric analysis because it was determined that the data was not normally distributed. Following adjustment for multiplicity, no statistically significant improvement, compared to placebo, was evident for any individual moderate to severe self-assessed vaginal symptom identified by the subject as being the most bothersome to her at baseline.

Two study populations of interest supported the original decision. In the non-parametric analysis of the mITT-1 study population (representing a subset of the mITT population who identified at baseline a most bothersome moderate to severe vaginal symptom and had a vaginal pH of ≥ 5.0 and a vaginal cytology with $\leq 5\%$ superficial epithelial cells), subjects treated with 10 mcg estradiol vaginal tablets for 12 weeks did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of any of the prespecified symptoms of VVA, including the VVA symptom of dyspareunia (p=0.020), when data was appropriately adjusted for multiplicity using a Bonferroni adjustment for multiple symptoms (vaginal dryness, vaginal irritation/itching, and dyspareunia). In the analysis of the mITT-2 study population (representing subjects who identified at baseline a moderate to severe most bothersome symptom of VVA, without consideration of their baseline vaginal pH value or the proportion of vaginal superficial epithelial cells on a vaginal smear), subjects treated with 10 mcg estradiol vaginal tablets also did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of any of the prespecified symptoms of VVA, including the VVA symptom of dyspareunia (p=0.116).

The Applicant, Novo Nordisk Inc. (100 College Road West, Princeton, NJ 08540) received a Complete Response letter on October 15, 2008 for sNDA 20-908/SE1-013.

Following a Type A meeting held on March 20, 2009, the Applicant was advised that "--- the Division acknowledges that the Applicant may not have fully understood the intent of the draft

Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom"---.", and that "--- the clinical deficiency regarding the efficacy of Vagifem (estradiol vaginal tablets) 10 µg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified primary analysis. The Division, however, will need to confirm that the Applicant's composite re-analysis for the most bothersome symptom supports a finding that treatment with Vagifem 10 µg is statistically superior to treatment with placebo."

2.6 Other Relevant Background Information

Vagifem® 25 mcg has been marketed in the United States since year 2000.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See the Chemistry, Manufacturing and Controls (CMC) Primary Review of sNDA 20-908/SE1-013 dated September 19, 2008, the CMC Re-Submission Review dated November 3, 2009, and the CMC Re-Submission Review Addendum dated November 19, 2009.

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted during the first review cycle regarding the container labels, carton and insert labeling for the drug product. DMEPA conducted a search of the Adverse Event Reporting System (AERS) database to identify any medication errors associated with the use of Vagifem® 25 mcg tablets. Per the consultation review, "Our AERS search retrieved three cases, two of which were related to either an adverse drug event or the quality of the drug product. In the remaining case, the reporter states that they may not have used the product correctly. No further details were provided about this case and this case appears to be an isolated event. It does not appear that the container labels, carton and insert labeling, nor the nomenclature contributed to any of the reported medication errors."

Per the DMEPA conclusions and recommendations, "The Label and Labeling Risk Assessment indicate that the presentation of information and design of the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval". DMEPA identified the following areas of needed improvement:

- "Replace all unit designations expressed as "µg" with "mcg" when expressed with a strength to be consistent with FDA's policy on excluding dangerous abbreviations and symbols from approved labels and labeling. FDA launched a campaign on June 14, 2006 warning health

care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g., trailing zeros).
- Consider revising the carton labeling so that the strength appears immediately following the dosage form. In its current location, it may be more difficult to locate the strength because it is inconsistent from what consumers and healthcare practitioners are used to.
- List the inactive ingredients on the carton labeling per 21 CFR 201.100 (b)(5).
- The numbering in the patient labeling for the instructions is confusing in presentation and the figures are not coordinated with the text. Consider labeling figures alphabetically and reserve the numbers for the instruction steps."

The DMEPA comments and recommendations were forwarded to Novo Nordisk Inc. on August 17, 2009. In a response received on September 18, 2009, the Applicant indicated the following:

"This submission contains the revised draft labels and labeling for Vagifem 10 µg as recommended by DMEPA as follows:

- "The unit designation "µg" has been replaced in all labels and labeling with "mcg"."
- "The enclosed carton labeling has been revised to move the (b)(4)
- "The inactive ingredients are now listed on the enclosed carton labeling."
- "The instructions in the patient labeling have been revised and the figures are listed alphabetically with numbers for the instruction steps."

Medical Officer's Comments:

Per the CMC Primary Review dated September 19, 2008, "Adequate information has been provided to support this supplement. Additionally, the Office of Compliance recommends the proposed manufacturing site for approval. This supplement, therefore, is recommended for approval."

Per the CMC Re-Submission Review dated November 3, 2009, "The DMETS reviewer provided comments regarding the container and carton, which the sponsor accepted." "The carton and container is acceptable from a CMC perspective." The CMC Re-Submission Review Addendum dated November 19, 2009 states, "This addendum clarifies that the responses to the Complete Response did not provide any new CMC information for review."

3.2 Animal Pharmacology/Toxicology

See the Pharmacology/Toxicology Primary Review of sNDA 20-908/SE1-013 dated May 21, 2008, and the Class 2 Re-Submission Review dated November 9, 2009.

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Medical Officer's Comments:

Per the Pharmacology/Toxicology Primary Review dated May 21, 2008, "Based on the approval of Vagifem (estradiol vaginal tablets) 25 µg, which has the same formulation and dosing schedule as Vagifem 10 µg, Pharmacology considers Vagifem (estradiol vaginal tablets) 10 µg safe for the proposed indication." "Pharmacology recommends approval of sNDA 20-908 for Vagifem (estradiol vaginal tablets) 10 µg."

Per the Pharmacology/Toxicology Re-Submission Review dated November 9, 2009, "The resubmission contains no new pharm/tox information and the original pharm/tox recommendation for approval of Vagifem 10 µg is unchanged."

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

See the Medical Officer's Primary Review of NDA 20-908/SE1-013, dated October 6, 2008, for a detailed description of the source of clinical data submitted in sNDA 20-908/SE1-013 on December 7, 2007.

Study VAG-2195 was a double-blind, randomized 2:1 (active drug: placebo), multi-center, placebo-controlled, parallel-group clinical trial. The two treatment groups were 10 mcg estradiol vaginal tablet (205 subjects) and placebo vaginal tablet (104 subjects for a total of 309 subjects) for a treatment period of 52 weeks. One subject randomized to the placebo treatment group did not receive study drug. Therefore, the safety population for Study VAG-2195 was comprised of 308 subjects. Two hundred thirty-four (76%, 234 of 309 randomized subjects) completed the clinical trial. Seventy-five (75) subjects discontinued Study VAG-2195 (24%, 75 of 309 randomized subjects; 41 subjects in the 10 mcg estradiol vaginal tablet treatment group and 34 subjects in the placebo vaginal tablet treatment group). Most subjects completed 41 weeks or more of treatment in Study VAG-2195 (81.5%, 167 of 205 treated subjects in the 10 mcg estradiol vaginal tablet treatment group and 71%, 73 of 103 treated subjects in the placebo vaginal tablet treatment group).

Study VAG-1748 (which was not included in the original submission) was an open-label, multi-center, non-US clinical trial conducted to assess the endometrial safety of the 10 mcg estradiol vaginal tablet. Healthy non-hysterectomized postmenopausal women ≥ 45 years of age, with serum FSH levels > 40 mIU/mL and estradiol levels < 20 pg/mL, and with at least one urogenital symptom of moderate to severe intensity were enrolled in Study VAG-1748. All subjects received active treatment. Using the supplied applicator, each randomized subject inserted one 10 mcg estradiol vaginal tablet once daily during the first two weeks of treatment followed by twice weekly administration for the remainder of the trial (50 weeks).

Endometrial biopsy specimens were evaluated at the beginning and end of Study VAG-1748. The primary safety endpoint for Study VAG-1748 was the hyperplasia rate at the end of the study at month 12 (week 52). Other safety endpoints included: vital signs, laboratory tests, physical examination, gynecological examination, Pap smear, transvaginal ultrasound (TVU), local tolerability of 10 mcg estradiol vaginal tablet, mammogram, and adverse events. Of the 336 subjects who received an endometrial biopsy at baseline, 283 completers received an endometrial biopsy at week 52. In total, 88.4% (297 of 336 subjects with baseline endometrial biopsies) of subject participating in Study VAG-1748 had end of treatment endometrial biopsies (including those subjects who prematurely discontinued the study). Forty-four (44) subjects discontinued Study VAG-1748: 18 subjects due to adverse events (41%, 18 of 44 discontinued subjects), 7 subjects due to non-compliance (16%, 7 of 44 discontinued subjects), 6 subjects due to ineffective therapy (14%, 6 of 44 discontinued subjects), and 13 subject due to other reasons (29%, 13 of 44 discontinued subjects).

4.2 Tables of Clinical Studies

Table 1 includes a brief overview of Study VAG-1850, Study VAG-2195, and Study VAG-1748.

Table 1: Overview of Studies VAG-1850, VAG-2195 and VAG-1748

Type of Study	Study Identifier	Objectives of Study	Study Design and Type of Control	Test Products, Dosage Regimen, Route of Administration	Number of Subjects: Total	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Bio-availability	VAG-1850 (U.S.)	To evaluate systemic estradiol absorption and safety	Single-center, randomized, open-label, multiple-dose, parallel-group trial Compare systemic absorption (plasma PK parameters) for 10 mcg estradiol vaginal tablet versus Vagifem 25 mcg tablet	**10 mcg tablet** Once daily for 2 weeks, followed by twice-weekly for 10 weeks **25 mcg tablet** Once daily for 2 weeks, followed by twice-weekly for 10 weeks	58 randomized 57 treated	Healthy postmenopausal women (60-70 years) with history of 5 years of amenorrhea or 2 years of surgical menopause with E2 <20 pg/mL and FSH >40 mIU/mL, with signs and symptoms of atrophic vaginitis.	12 weeks (2 weeks once-daily, 10 weeks twice-weekly)

Type of Study	Study Identifier	Objectives of Study	Study Design and Type of Control	Test Products, Dosage Regimen, Route of Administration	Number of Subjects: Total	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Efficacy	VAG-2195 (U.S., Canada)	Efficacy and safety	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial Compared clinical efficacy and endometrial safety of 10 mcg estradiol vaginal tablet versus placebo vaginal tablet	**10 mcg tablet** Once daily for 2 weeks, followed by twice-weekly for 50 weeks **Placebo** Once daily for 2 weeks, followed by twice-weekly for 50 weeks	309 randomized 308 treated 234 completed	Healthy postmenopausal women (45 years or older) ≥2 years after last menstruation; or bilateral oophorectomy performed ≥2 years before screening, with E2 <20 pg/mL and FSH <40 mIU/mL, ≤5 percent superficial cells, vaginal pH >5, endometrial thickness <4.0 mm and normal mammograms. Subjects had ≥3 urogenital symptoms and at least one of them had to be a moderate to severe symptom as identified by the patient.	52 weeks (2 weeks once-daily, 50 weeks twice-weekly)
Safety	VAG-1748 (Czech Republic, Denmark, Finland, France, Hungary, Norway, and Sweden)	Safety	Open-label, multicenter, 12 month study to evaluate the endometrial safety of 10 mcg estradiol vaginal tablet in the treatment of postmenopausal atrophic vaginitis	**10 mcg tablet** Once daily for 2 weeks, followed by twice-weekly administration for 50 weeks	336 treated 292 completed	Healthy postmenopausal women ≥ 45 years of age, ≥ 2 years spontaneous amenorrhea or post-oophorectomy, FSH levels > 40 mIU/mL, estradiol < 20 pg/mL, with at least one urogenital symptom of moderate to severe severity. ≤ 5% superficial cells, vaginal pH > 5, and endometrial thickness < 4 mm	52 weeks (2 weeks once-daily, 50 weeks twice-weekly)

Source: Adapted from the December 7, 2007 submission and the Integrated Summary of Safety (ISS) submitted to NDA 20-908/SE1-013 dated July 2, 2009, page 6 of 26.
Definitions: mcg = microgram, E2 = estradiol, FSH = follicle stimulating hormone.

4.3 Review Strategy

The primary source of efficacy data submitted in support of the treatment of atrophic vaginitis due to menopause is Phase 3a Study VAG-2195.

The primary source of safety data in the re-submission is Phase 3a Study VAG-2195 and safety Study VAG-1748. The original safety data received on December 7, 2007 (sNDA 20-908/SE1-013), the safety data received in the Class 2 re-submission on May 26, 2009, and the Integrated Safety Summary of endometrial biopsy results received on July 2, 2009 report the treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, subject withdrawals, clinical laboratory parameters, vital sign measurements, transvaginal ultrasound (TVU) results, and endometrial biopsy results for the 12-month Studies VAG-2195 and VAG-1748.

The safety update included in the May 26, 2009 re-submission states the following:

- "There are no ongoing nonclinical and/or clinical studied/trials of Vagifem 25 or 10 mcg."
- "There are no new safety data from completed studies VAG-2195 and VAG-1850 since the 120 Day Safety Update submitted on April 3, 2008."

On May 28, 2009, Novo Nordisk submitted a Periodic Safety Update Report (PSUR) for Vagifem® 25 mcg for the period April 1, 2008 – March 31, 2009. Vagifem® 25 mcg is now approved in 75 countries. Per the May 28, 2009 submission, "There have been no rejections or restrictions to distribution for safety reasons during the reporting period. No actions have been taken for safety reasons during the reporting period."

4.4 Data Quality and Integrity

See the Medical Officer's Primary Review of sNDA 20-908/SE1-013, dated October 6, 2008, for a detailed description of data quality and integrity for Study VAG-2195.

In general, DSI stated during the original review cycle that "for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoints captured as specified in the protocol."

4.5 Compliance with Good Clinical Practices

The primary, Phase 3a, safety and efficacy Study VAG-2195 and the safety Study VAG-1748 appear to have been conducted in accordance with regulations pertaining to Good Clinical Practice (GCP), the International Conference on Harmonization: Good Clinical Practice Consolidation Guidelines, the Code of Federal Regulations (Notice of Availability, *Federal Register* 25692, May 6, 1997), and the Declaration of Helsinki (revised Hong Kong, 1989).

Written informed consent was obtained before subject enrollment. Each subject was assigned a subject number, which was used on the case report form (CRF) instead of the subject's name.

4.6 Financial Disclosures

See the Medical Officer's Primary Review of sNDA 20-908/SE1-013, dated October 6, 2008, for information regarding financial disclosures for the pivotal Phase 3a clinical trial (Study VAG-2195).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See the Clinical Pharmacology Primary Review of sNDA 20-908/SE1-013, dated July 17, 2008, for a detailed discussion of Phase 1 Study VAG-1850. See also the Clinical Pharmacology Re-Submission Review dated October 15, 2009, and the Clinical Pharmacology Re-Submission Review Addendum dated November 20, 2009.

Medical Officer's Comments:

Per the Clinical Pharmacology Re-Submission Review dated October 15, 2009, the "Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed the Clinical Pharmacology related sections of the proposed product labeling in this resubmission for NDA 20-908/S-013 submitted May 26, 2009, July 9, 2009, and September 18, 2009. The overall Clinical Pharmacology information submitted to support the NDA is acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language."

The Clinical Pharmacology Re-Submission Review Addendum, dated November 20, 2009, addresses the Clinical Pharmacology related labeling changes. Per this review, "There are no outstanding Clinical Pharmacology issues."

5.2 Pharmacodynamics

No pharmacodynamic studies related to efficacy were conducted for the 10 mcg estradiol vaginal tablet.

5.3 Exposure-Response Relationships

An increased incidence of shifts from baseline TVU measurements < 4 mm to > 4 mm was observed in Study VAG-2195 and Study VAG-1748 for the 10 mcg estradiol vaginal tablet. These findings are discussed further in Section 7.1.3 "Dropouts and Other Significant Adverse Events" of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Vagifem® (estradiol vaginal tablets) 25 mcg is currently approved for the treatment of atrophic vaginitis.

The sNDA 20-908/SE1-013 re-submission is seeking approval of the 10 mcg estradiol vaginal tablet (administered intravaginally daily for 2 weeks followed by twice-weekly administration) for the proposed indication of "(b)(4) (b)(4)".

6.1.1 Methods

The clinical program to evaluate the safety and efficacy of the 10 mcg estradiol vaginal tablet included the single, randomized, double-blind, placebo-controlled, 12-month, Phase 3a Study VAG-2195. The re-analysis of data submitted for primary Phase 3a Study VAG-2195 will be discussed further in this review. Study VAG-1748 contributes additional safety data for the 10 mcg estradiol vaginal tablet.

6.1.2 General Discussion of Endpoints

See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of endpoints for a VVA indication.

Per the Agency's 2003 draft clinical evaluation guidance document, the Agency recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that evaluate the following three co-primary endpoints for a VVA indication:

- The mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells).

- The mean change from baseline to week 12 in vaginal pH.

- The mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her.

A statistically significant improvement versus placebo from baseline to week 12 in all three of the co-primary endpoints must be demonstrated for a product to be considered for approval for a [redacted](b)(4)

Medical Officer's Comments:

The intent of the Agency's 2003 draft clinical evaluation guidance document for the third listed co-primary endpoint (mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her) is to demonstrate statistically significant improvement in one or more individual moderate to severe most bothersome symptom(s) identified and not to combine all moderate to severe most bothersome symptoms into a composite analysis. Thus, the individual vaginal symptom(s) that demonstrates statistically significant improvement between baseline and week 12 would then be [redacted](b)(4).

During drug development, DRUP is careful to clarify that the mean change between baseline and week 12 for each individual moderate to severe most bothersome symptom should be analyzed. In the development of the 10 mcg estradiol vaginal tablet, however, it is possible that the intent of the guidance document was not clearly conveyed to the Applicant regarding the third co-primary endpoint.

The primary efficacy analysis that DRUP has been recommending since the Agency's 2003 draft clinical evaluation guidance document was issued is that the efficacy analysis be based on a modified intent-to-treat (mITT) population. This mITT population consists of subjects who: (1) receive at least one dose of study drug, (2) have a baseline and at least one post-baseline efficacy evaluation, and (3) at baseline identify a moderate to severe most bothersome symptom and have a vaginal pH of 5.0 or greater and a vaginal cytology of 5% or less superficial cells on a vaginal smear (referred to as the mITT-1 study population in this review). This mITT-1 study population most closely reflects symptomatic postmenopausal women with physical findings of vulvar and vaginal atrophy (for example, a vaginal pH greater than 5.0 and more than 5% superficial cells on a vaginal smear).

Medical Officer's Comments:

In the first review cycle of NDA 20-908/SE1-013, a second efficacy analysis of the mITT population was performed for subjects who: (1) received at least one dose of study drug, (2) had a baseline and at least one post-baseline efficacy evaluation, and (3) at baseline identified a moderate to severe most bothersome symptom without consideration of their baseline vaginal pH and vaginal cytology (referred to as the mITT-2 study population in this review). It was determined that this mITT-2 study population was "closer" to the Applicants protocol-specified ITT population defined as "all randomized subjects who take at least one dose of trial

medication and have baseline and one post-baseline efficacy assessment for any efficacy parameter." The Applicant's protocol-specified ITT analysis will be discussed further in this review.

6.1.3 Study Design

See the Medical Officer's Primary Review of sNDA 20-908/SE1-013, dated October 6, 2008, for a detailed description of the study design implemented in Phase 3a Study VAG-2195. Study VAG-2195 was the primary source of safety and efficacy data. The primary efficacy endpoints in Study VAG-2195 were the mean change from baseline to week 12 in: (1) vaginal Maturation Index and Maturation Value, (2) vaginal pH, and (3) the moderate to severe symptom that was identified by the patient as being most bothersome to her at baseline.

In the original protocol for Study VAG-2195 (submitted under IND (b)(4) and received on (b)(4)), the ITT study population was defined as "all randomized subjects who take at least one dose of trial medication and have baseline and at least one post-baseline efficacy assessment for any efficacy parameter." The primary efficacy endpoint was "the change from baseline to week 12 of the average score of 3 vaginal symptoms (dryness, soreness, and irritation), 2) Vaginal Maturation Value, and 3) vaginal pH. Severity of symptoms is measured at every treatment visit and the screening visit as well. Intent to treat (ITT) analysis with the "last observation carried forward" (at week 12) will be performed." "Vaginal cell maturation data will be recorded as percentages of parabasal, intermediate, and superficial cells." "Vaginal pH is recorded within four intervals (< 5, 5–5.49, 5.5-6.49, and > 6.49)."

Regarding symptom relief, the original protocol stated, "--- the symptoms associated with atrophic vaginitis are dryness, soreness, irritation, dyspareunia, and vaginal discharge. Each item is graded on a 4 point scale (none, mild, moderate, severe). Scores are assigned to each grade as 0, 1, 2, and 3, respectively. An average score of 3 vaginal symptoms (dryness, soreness, and irritation) will be calculated. Analysis of covariance (ANCOVA) will be used for the between group comparison in analyzing the symptoms data with treatment and centre included as fixed effects and corresponding baseline value as a covariate. These analyses will be performed on change from baseline scores at week 2, week 4, week 8, week 12, week 12 (LOCF), week 26, week 39, and week 52. Due to the large number of centres (> 50) to be used in this study, treatment-by-centre interaction effect may be explored, but not included in the final model. With a sample size of this magnitude, the robustness of the ANCOVA model can reasonably be assured by the central limit theory, without the normality assumption. The same (ANCOVA) model will be used to analyze maturation value and vaginal pH." Other efficacy endpoints discussed in the original protocol included, but are not limited to, "--- the average score of five vaginal symptoms (dryness, soreness, irritation, dyspareunia and vaginal discharge)."

In Amendment 1 to the original protocol, received on March 11, 2005, the following changes were identified, but were not limited to:

- Section 3.4 Primary Endpoints changed to:

"Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
Mean change from baseline to week 12 in Vaginal pH
Mean change from baseline to week 12 in the Vaginal Maturation Index and Value"

- Section 3.4 Other Endpoints changed to:

  "Clinical vaginal symptoms: dryness, soreness, irritation (an average of three vaginal symptoms)
  Change from baseline to week 12 in grading of vaginal health (vaginal secretions, epithelial integrity, epithelial surface thickness, vaginal color and pH)
  Mean change from baseline to week 12 in the Urethral Maturation Index and Value"

- Section 5.2 Inclusion Criterion # 5 changed to:

  "Subjects should have at least three urogenital symptoms and at least one of them has to be a moderate to severe symptom as identified by the subject (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia and vaginal bleeding associated with sexual activity) during the last week of the screening period."

- Section 15 Statistical Considerations, 15.2.2 Primary Endpoints changed to:

  "The primary efficacy endpoints are the mean change from baseline to week 12 in 1) the moderate to severe symptom that has been identified by the patient as being most bothersome to her, 2) vaginal maturation Index (parabasal and superficial cells) and Value, and 3) vaginal pH. Intent to treat (ITT) analysis with the "last observation carried forward" (LOCF) at (week 12) will be performed."

- Section 15 Statistical Considerations, 15.2.2 Symptom Relief changed to:

  "The symptoms associated with atrophic vaginitis are vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, pain associated with sexual activity (dyspareunia) and bleeding associated with sexual activity. Each item is graded on a 4 point scale (none, mild, moderate, severe). Scores are assigned to each grade as 0, 1, 2, and 3, respectively."

- Section 15 Statistical Considerations, 15.2.4 Other Efficacy Endpoints changed to:

  "The other efficacy endpoints are grading of vaginal health by the investigator, urethral cytology, and the average score of three vaginal symptoms (dryness, soreness, and irritation/itching) as well as the 6 individual symptoms. These endpoints are measured at treatment visits: baseline, weeks 2, 4, 8, 12 and 52."

In protocol Amendment 2 submitted February 24, 2006, the total number of subjects to be enrolled in Phase 3a Study VAG-2195 was reduced from 600 subjects (400 subjects treated with

10 mcg estradiol vaginal tablets and 200 subjects treated with placebo vaginal tablets) to 300 subjects (200 subjects treated with 10 mcg estradiol vaginal tablets and 100 subjects treated with placebo vaginal tablets) due to "slow patient enrollment". Per the submission, however, a sample size of 200 subjects treated with 10 mcg estradiol vaginal tablets and 100 subjects treated with placebo vaginal tablets would provide "90% power to detect a difference of 0.48 in change from baseline to Week 12 for the relief of urogenital symptoms (based on the most bothersome symptom score of dryness, irritation/itching, soreness, dysuria, pain associated with sexual activity, and bleeding associated with sexual activity), with an estimated standard deviation of 1.1 in change from baseline to 12 weeks." The sample size would provide "90% power to detect a difference of 7.2% with estimated standard deviation 16.5% in change from baseline to 12-week score for vaginal cytology ─ Parabasal Cell (%) and to detect a difference of 8.6% with estimated standard deviation 19.7% in change from baseline to 12-week score for vaginal cytology ─ Superficial Cell (%)." For vaginal pH, the sample size would provide "90% power to detect a difference of 0.44 with estimated standard deviation 1.0 in change from baseline to 12 weeks." Per the submission, this estimated sample size was based on a 2-sided significance level of 0.05 and included a 15% dropout rate.

6.1.4 Efficacy Findings

See the Medical Officer's Primary Review dated October 6, 2008 and the Statistical Primary Review dated October 8, 2008 for a detailed description of the efficacy data submitted, either in the original submission or upon request of DRUP, and reviewed during the first review cycle. See also the Medical Team Leader's Primary Review dated October 7, 2008 and the Division Director's Primary Review dated October 14, 2008.

The Complete Response regulatory action of October 15, 2008 was based on the non-parametric analysis of the data from primary Phase 3a Study VAG-2195 for two study populations: (1) the mITT-1 study population (representing a subset of the mITT population [defined as all randomized subjects who take at least one dose of trial medication and have baseline and one post-baseline efficacy evaluation] who identified at baseline a most bothersome moderate to severe vaginal symptom and had a vaginal pH of ≥ 5.0 and a vaginal cytology with $\leq 5\%$ superficial epithelial cells), and (2) the mITT-2 study population (representing subjects who identified at baseline a moderate to severe and most bothersome symptom of VVA, without consideration of their baseline vaginal pH value or the proportion of vaginal superficial epithelial cells on a vaginal smear).

Per the Agency's 2003 draft clinical evaluation guidance document, the mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her is one of three recommended co-primary endpoints. In the analysis of the mITT-1 study populations, subjects treated with 10 mcg estradiol vaginal tablets for 12 weeks did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual VVA symptom, including the VVA symptom of dyspareunia ($p=0.020$), when the analysis was appropriately adjusted for multiplicity using a Bonferroni adjustment for the primary analysis of multiple symptoms

(choice of three symptoms of dryness, irritation, and dyspareunia) (p=0.05 ÷ 3 = 0.016). In the analysis of the mITT-2 study population, subjects treated with 10 mcg estradiol vaginal tablets also did not demonstrate a statistically significant greater reduction, compared to placebo treatment, in the severity of at least one individual VVA symptom, including the VVA symptom of dyspareunia (p=0.116).

Vaginal Maturation Index:

Based on the Applicant's reported mean change in the proportion of superficial and parabasal cells between baseline and week 12 in the ITT study population, treatment with 10 mcg estradiol vaginal tablet statistically increased the mean percentage of superficial cells from baseline to week 12 (p< 0.001) and statistically decreased the mean percentage of parabasal cells from baseline to week 12 (p< 0.001) compared to the placebo vaginal tablet. See Table 2.

Table 2: Analysis of Vaginal Maturation Index for the ITT Study Population in Study VAG-2195

Parameter	**10 mcg Estradiol Vaginal Tablet**		**Placebo Vaginal Tablet**		
Visit	N	Mean	N	Mean	**p-value**
Parabasal Cells (%)					
Baseline	198	41.8	102	43.4	-
Change from Baseline to Week 12 (LOCF)	195	-37.0	102	-9.3	<0.001
Superficial Cells (%)					
Baseline	198	3.3	102	2.5	-
Change from Baseline to Week 12 (LOCF)	195	13.2	102	3.8	<0.001

Source: Adapted from sNDA 20-908/SE1-013 December 7, 2007 submission and the Request for Meeting submission, dated January 9, 2009, Table 1, Efficacy Summary- ITT Population, page 9 of 12.

Vaginal pH;

Based on the Applicant's reported mean change in the vaginal pH score between baseline and week 12 in the ITT study population, treatment with 10 mcg estradiol vaginal tablet demonstrated a statistically significant decrease in the vaginal pH score from baseline to week 12 (p< 0.001) compared to the placebo vaginal tablet. See Table 3.

Table 3: Analysis of Vaginal pH Score for the ITT Study Population in Study VAG-2195*

	10 mcg Estradiol Vaginal Tablet		Placebo Vaginal Tablet		
Visit	N	Mean	N	Mean	**p-value**
Baseline	204	2.3	102	2.4	-
Change from Baseline to Week 12 (LOCF)	202	-1.3	102	-0.4	<0.001

Source: Adapted from sNDA 20-908/SE1-013 December 7, 2007 submission and the Request for Meeting submission, dated January 9, 2009, Table 1, Efficacy Summary- ITT Population, page 9 of 12.

* In Study VAG-2195 the observed reading of the vaginal pH test strip were recorded within four intervals, as a score (not a calculated value) corresponding to pH < 5.0 = 0 (no atrophy), pH 5-5.49 = 1 (mild atrophy), pH 5.5-6.49 = 2 (moderate atrophy), or pH > 6.49 = 3 (severe atrophy).

Medical Officer's Comments:

This reviewer concurs with the use of a vaginal pH score in sNDA 20-908/SE1-013. A pH score is consistent with labeling for the approved Vagifem® 25 mcg drug product.

Most Bothersome Vulvar and Vaginal Atrophy Symptom:

During the first review cycle, after adjusting for multiplicity, the reported findings for the symptom of dyspareunia for the mITT-1 population did not demonstrate a statistically significant improvement for the 10 mcg estradiol vaginal tablet as compared with the placebo vaginal tablet (p=0.020). The reported findings for the symptom of dyspareunia for the mITT-2 population also did not demonstrate a statistically significant improvement for the 10 mcg estradiol vaginal tablet as compared with the placebo vaginal tablet (p=0.116).

Medical Officer's Comments:

DRUP and the Applicant communicated numerous times during the first review cycle regarding the DRUP-defined mITT-1 and mITT-2 study population non-parametric analyses and adjustment for multiplicity for the third co-primary endpoint of mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her.

Following the Complete Response letter dated October 15, 2009, and the subsequent meeting with the Applicant held on March 20, 2009, DRUP offered the following post-meeting comments and recommendations:

1. *"Based on the discussion and clarification provided by Novo Nordisk, the Division acknowledges that the Applicant may not have fully understood the intent of the draft Guidance Document regarding the analysis for the co-primary endpoint of the "most bothersome symptom" prior to the Division's letter of September, 2007."*
2. *"The Division believes that the clinical deficiency regarding the efficacy of Vagifem (estradiol vaginal tablets) 10 µg described in the Complete Response letter of October 15, 2008, could be addressed by re-analysis of the existing data, based on the protocol-specified*

primary analysis. The Division, however, will need to confirm that the Applicant's composite re-analysis for the most bothersome symptom supports a finding that treatment with Vagifem 10 µg is statistically superior to treatment with placebo."

Based on these comments and recommendations, DRUP agreed to consider a re-analysis of a composite of all most bothersome symptoms in support of a finding that treatment with 10 mcg estradiol vaginal tablet demonstrated statistically significant improvement over treatment with placebo in the treatment of atrophic vaginitis.

The May 26, 2009 re-submission presented a re-analysis of a composite of all most bothersome symptoms, between baseline and week 12, for the 10 mcg estradiol vaginal tablet versus the placebo vaginal tablet. The re-analysis demonstrates a statistically significant difference (p=0.002) in the mean change from baseline for the 10 mcg estradiol vaginal tablet compared to the placebo vaginal tablet at week 12 (LOCF). See Table 4.

Table 4: Mean Change from Baseline to Week 12 in a Composite Score of Most Bothersome Symptoms Compared to Placebo – ITT Population[a]

	10 mcg Estradiol Vaginal Tablet		**Placebo Vaginal Tablet**		
Visit	N	Mean	N	Mean	**p-value**
Baseline	190	2.29	93	2.35	-
Change from Baseline to Week 12 (LOCF)	190	-1.20	93	-0.84	0.002

[a] All randomized subjects who received at least one dose of study drug and had a baseline and at least one post-baseline assessment using last observation carried forward (LOCF) for those subjects discontinuing prematurely.

Medical Officer's Comments:

Per the Statistical Re-Submission Review, dated November 20, 2009, "The study results support the efficacy of Vagifem (10 mcg estradiol vaginal tablets) in the treatment of atrophic vaginitis due to menopause. Treatment with Vagifem resulted in a statistically significant reduction in (1) a composite score of all most bothersome symptoms, (2) vaginal pH, and (3) the percentage of parabasal cells compared to treatment with placebo at week 12. A statistically significant increase in superficial cells for treatment compared to placebo at week 12 was also demonstrated."

"From a statistical perspective, the results demonstrate the efficacy of Vagifem 10 mcg in the treatment of atrophic vaginitis due to menopause."

The Statistical Re-Submission Review, dated November 20, 2009, also addresses a DRUP requested change in the labeling submitted under sNDA 20-908/SE1-013 for the presentation of the efficacy data for Vagifem® 25 mcg. In the labeling submitted under sNDA 20-908/SE1-013, efficacy data for the Vagifem® 25 mcg dosage strength is presented in the graphical format that appears in the current approved labeling for Vagifem® 25 mcg. The Division requested that the Applicant change the Vagifem® 25 mcg graphical format presentation to a tabular format

presentation (to include mean change from baseline to week 7 [LOCF] and week 12 [LOCF]) to maintain consistency with the tabular data presented for the 10 mcg estradiol vaginal tablet as shown in Table 4. On November 17, 2009, the Applicant submitted a tabular presentation for the Vagifem® 25 mcg dosage strength along with the datasets for pivotal Phase 3 Study VAG/PD/9/USA.

Per the Statistical Re-Submission Review, dated November 20, 2009, "We verify these efficacy results---." "At week 7 and week 12, treatment with Vagifem 25 mcg also demonstrated statistically significant reduction in a composite of most bothersome symptoms."

6.1.5 Clinical Microbiology

Per the Chemistry, Manufacturing and Controls Primary Review, dated September 19, 2008, Study VAG-2195 used drug product manufactured with the approved chemistry, manufacturing and controls. No clinical microbiology consult is needed for sNDA 20-908/SE1-013.

6.1.6 Efficacy Conclusions

The results from the re-analyses for the Applicant's defined ITT study population, based on a composite of all most bothersome symptoms (combined with the results of the analyses of vaginal pH score and vaginal superficial and parabasal cells) for the first 12 weeks of double-blind Phase 3a Study VAG-2195 demonstrates statistically significant effectiveness for the 10 mcg estradiol vaginal tablet versus the placebo vaginal tablet for the treatment of atrophic vaginitis due to menopause.

The reviewer recommends that the 10 mcg estradiol vaginal tablet be approved for the treatment of atrophic vaginitis due to menopause. The indication, "treatment of atrophic vaginitis" is the indication in approved labeling for the Vagifem® 25 mcg tablet. The efficacy findings for the Applicant's defined ITT study population of a composite of all most bothersome symptoms for the 10 mcg estradiol vaginal tablet closely reflect the efficacy findings for the ITT population of a composite score of symptoms for the approved Vagifem® 25 mcg tablet. The composite analysis, however, does not support the (b)(4) in labeling.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of the safety evaluations and findings in 52-week, Phase 3a Study VAG-2195 and supportive Phase 1 Study VAG-1850.

The May 26, 2009 re-submission contained the final clinical trial report for completed non-IND Study VAG-1748 entitled "A 12-month open label multicenter trial to investigate the endometrial safety of Vagifem Low Dose (10 µg 17 beta-estradiol tablet) in postmenopausal women with atrophic vaginitis symptoms". Study VAG-1748 was conducted in the Czech Republic, Denmark, Finland, France, Hungary, Norway, and Sweden. The primary objective of Study VAG-1748 was:

- "to evaluate the endometrial safety of Vagifem 10 µg in the treatment of postmenopausal atrophic vaginitis symptoms".

"The primary safety endpoint was the hyperplasia rate at the end of study (Week 52). Endometrial biopsies were taken at the beginning and end of the study." "The endometrial hyperplasia rate at the end of 12-month treatment was to be calculated based on all subjects who received at least one dose of medication and had an interpretable endometrial biopsy result at Week 52."

"Other safety evaluations of Vagifem 10 µg consisted of standard physical and gynecological examinations, vital signs, routine clinical laboratory tests, and adverse events."

7.1.1 Deaths

No deaths occurred in primary Phase 3a Study VAG-2195 or in Phase 1 Study VAG-1850. One death occurred during the conduct of non-IND 52-week Study VAG-1748. Subject (b)(6), a 77 year old postmenopausal woman treated in France received 10 mcg estradiol vaginal tablets between (b)(6) and (b)(6) (approximately 9 months of treatment) and died on (b)(6). She was diagnosed with cerebral metastasis of a primary unknown cancer. An autopsy was not performed. Screening procedures for Subject (b)(6) were reported as negative for breast, endometrium, and cervix. The investigator and Novo Nordisk Inc. assessed the relationship causality of the event as unlikely related given the "advanced stage cancer of unknown primary location after only 9 months of treatment".

7.1.2 Other Serious Adverse Events

Seven (7) subjects (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [2.4%, 5 of 205 treated subjects] and 2 subjects in the placebo vaginal tablet treatment group [2%, 2 of 103 treated subjects]) in Study VAG-2195 reported serious adverse events (SAEs). The nature of these SAEs is reported in the Medical Officer's Primary Review dated October 6, 2008.

No SAEs were reported in 12-week Phase 1 Study VAG-1850.

Fourteen (14) subjects experienced SAEs in non-IND Study VAG-1748 (4.2%, 14 of 336 subjects treated with 10 mcg estradiol vaginal tablets). The nature of these 14 SAEs are shown below.

Subject ID (b)(6)	Serious Adverse Event
	Abdominal pain (small intestine enteritis), hypokalemia, and anemia
	Melena
	Cholelithiasis with cholecystectomy
	Fracture of right wrist (radius and ulna, distal)
	Fracture of left wrist (radius)
	Abdominal plastic surgery (hematoma, postoperative infection)
	Back pain (spinal stenosis)
	Neck mass (recurrence of leukemia)
	Metastatic cancer (cerebral metastasis of a primary unknown cancer)
	Brain tumor (meningioma)
	Rectal bleeding (adenoma tubulovillosum flexurae leinalis coli)
	Brain infarction (thrombotic cerebral infarction)
	Urine incontinence (worsening)
	Thoracic pain (myocardial infarction)

The safety update included in this May 26, 2009 re-submission provides the following information:

- "There are no ongoing nonclinical and/or clinical studied/trials of Vagifem 25 or 10 mcg."
- "There are no new safety data from completed studies VAG-2195 and VAG-1850 since the 120 Day Safety update submitted on April 3, 2008."

Medical Officer's Comments:

In total, 21 subjects (3.3%, 21 of 644 treated subjects in combined Studies VAG-2195 and VAG-1748) experienced serious adverse events during the conduct of these two 52-week studies (Study VAG-2195 = 5 subjects in the 10 mcg estradiol vaginal tablet treatment group [2.4%, 5 of 205 subjects] and 2 subjects in the placebo vaginal tablet treatment group [2%, 2 of 103 subjects]; and Study VAG-1748 = 14 subjects receiving 10 mcg estradiol vaginal tablets [4.2%, 14 of 336 treated subjects]). Overall, the number of subjects experiencing SAEs in these two 52-week studies is low. The 21 reported SAEs do not raise safety issues for the 10 mcg estradiol vaginal tablet.

7.1.3 Dropouts and Other Significant Adverse Events

Fifteen (15) treated subjects discontinued from Study VAG-2195 due to an adverse event, 11 (5%) in the 10 mcg estradiol vaginal tablet treatment group and 4 (4%) in the placebo vaginal tablet treatment group. One subject discontinued from 12-week Phase 1 Study VAG-1850.

See the Medical Officer's Primary Review, dated October 6, 2008, for the treatment group, subject number and day to onset, and adverse event reported for the 15 treated subjects who discontinued in Study VAG-2195 and the single subject who discontinued in Study VAG-1850.

Eighteen (18) subjects discontinued from Study VAG-1748 due to an adverse event.

Subject ID (days on study to onset)	Adverse event
10 mcg estradiol vaginal tablet	
(b)(6) (onset not available)	Vertigo, breast pain, muscle spasm
(day56)	Hypertension
(day 121)	Edema, headache, skin disorder
(day 1)	Recurrent leukemia
(day 148)	Vaginal spotting
(day 44)	Arrhythmia
(onset not available)	Metastases to central nervous system of primary unknown cancer
(b)(6) (day 31)	Myocardial infarction
(day 42)	Hypertension
(day 52)	Headache
(day 8)	Abdominal pain
(day 359)	Urinary incontinence
(day 265)	Vulvovaginal discomfort
(day113)	Acne
(day 2-3)	Vaginal discharge, pruritus, headache, pelvic pain, depression
(b)(6) (day 4)	Nausea, headache, hyperhidrosis
(day 236)	Breast tenderness
(day 132)	Vulvovaginal discomfort

Medical Officer's Comments:

As shown above, the reported adverse events resulting in discontinuation in 52-week Study VAG-1748 are commonly associated with estrogen therapy (for example, headache, breast tenderness, vaginal spotting, vaginal discharge, abdominal/pelvic pain, nausea, and vulvovaginal discomfort) and are not unexpected for estrogen-alone drug products.

Overall, the incidence of discontinuations due to an adverse event in Study VAG-2195 and Study VAG-1748 is low and does not raise safety issues.

7.1.3.1 Overall profile of dropouts

Three hundred and eight (308) subjects made up the safety population in Study VAG-2195. Fifteen (15) subjects discontinued from Study VAG-2195 due to an adverse event (4.8%, 15 of 308 treated subjects). Eleven (11) of these 15 subjects were treated with 10 mcg estradiol vaginal tablets (5.3%, 11 of 205 treated subjects). Four (4) of these 15 subjects were treated with placebo vaginal tablets (3.8%, 4 of 103 treated subjects).

Fifty-seven (57) subjects made up the safety population in Study VAG-1850. Of the 58 subjects randomized, 1 subject discontinued prior to the administration of study medication due to elevated liver enzymes determined during screening. One other subject (Subject (b)(6)), randomized to the Vagifem® 25 mcg treatment group, was withdrawn for non-compliance with study medication on day 7. A total of 56 subjects completed treatment in Study VAG-1850.

Three hundred and thirty-six (336) subjects made up the safety population in Study VAG-1748. Eighteen (18) subjects discontinued from Study VAG-1748 due to an adverse event (5.3%, 18 of 336 treated subjects). All subjects in Study VAG-1748 were treated with 10 mcg estradiol vaginal tablets.

7.1.3.2 Adverse events associated with dropouts

See Section 7.1.3 "Dropouts and Other Significant Adverse Events".

Three subjects with serious adverse events discontinued Study VAG-2195:

Subject (b)(6)= 57 years of age, 10 mcg estradiol vaginal tablet treatment group, hospitalized due to pneumonia, recovered.

Subject (b)(6)= 62 years of age, 10 mcg estradiol vaginal tablet treatment group for 324 days, endometrial biopsy diagnosis of adenocarcinoma with FIGO Grade 2 pattern (Nuclear grade = 1 and Architectural grade = 2), hospitalized for total hysterectomy and bilateral salpingo-oophorectomy with bilateral pelvic lymphadenectomy, post-surgery radiation therapy with radioactive implants to the vaginal area.

Subject (b)(6) = 55 years of age, placebo vaginal tablet treatment group for 54 days, hospitalized due to chest pain, stent replacement, recovered.

No treated subjects discontinued from Study VAG-1850 due to an adverse event.

Five subjects with serious adverse events discontinued Study VAG-1748;

Subject (b)(6) = 62 years of age, treated with trial drug from (b)(6), hospitalized for spinal stenosis, 4 pins inserted, recovered.

Subject (b)(6) = 77 years of age, treated with trial drug (b)(6), diagnosed with cerebral metastasis of a primary unknown cancer, died on (b)(6) (b)(6)

Subject (b)(6) = 62 years of age, treated with trial drug from (b)(6) (b)(6), thrombotic cerebral infarction, recovering.

Subject (b)(6) = 55 years of age, treated with trial drug from (b)(6) (b)(6) worsening of urinary incontinence, hospitalized and had incontinence band inserted, recovered.

Subject (b)(6) = 68 years of age, treated with trial drug from (b)(6), hospitalized for myocardial infarction, received coronary artery stents, recovered.

Medical Officer's Comments:

For Subject (b)(6) and Subject (b)(6) in Study VAG-2195, the Applicant listed the relationship to study drug as "unlikely". For Subject (b)(6), the Applicant listed causality as "possible".

The Applicant considered causality as "unlikely" for all of the SAEs listed for Study VAG-1748.

7.1.3.3 Other significant adverse events

Endometrial Thickness:

All subjects in Study VAG-2195 and Study VAG-1748 had a transvaginal ultrasound (TVU) performed prior to an endometrial biopsy at screening and at week 52 (or sooner if clinically indicated or at early termination). Per the study protocol, subjects whose double-wall endometrial thickness measured by TVU were > 4 mm at screening were not eligible for enrollment.

Per the original December 7, 2007 submission, the mean endometrial thickness at baseline in Study VAG-2195 was 2.20 mm in the placebo-treated group and 2.31 mm in the 10 mcg estradiol-treated group. After 52 weeks of treatment, mean endometrial thickness was 2.21 in the placebo-treated group and 2.47 mm in the 10 mcg estradiol-treated group.

In 12-week Study VAG-1850, TVUs were only obtained at screening to fulfill the inclusion criteria – "Endometrial thickness < 4.0 mm (double layer), as measured by transvaginal ultrasound (if applicable)".

Per the May 26, 2009 re-submission which included the final clinical trial report for Study VAG-1748, the mean endometrial thickness at baseline was 2.04 mm (334 of 336 subjects had a baseline TVU performed), 1.94 mm at week 52 (293 subjects had a week 52 TVU performed), and 1.94 mm at end-of treatment (LOCF) for 314 subjects.

A total of twenty-five (25) subjects had a TVU double-wall endometrial thickness ≥ 4 mm at week 52 or at early termination in Study VAG-2195 (21 subjects in the 10 mcg estradiol vaginal tablet treatment group and 4 subjects in the placebo vaginal tablet treatment group). The following presentation demonstrates the TVU information available for these 25 subjects.

Subjects treated with 10 mcg estradiol vaginal tablet:

Subject ID	Screening TVU	End-of-Study TVU	Other Findings
(b)(6)	3.0 mm (day -19)	5 mm (day 367)	None
	3.5 mm (day -14)	5 mm (day 363)	None
	2 mm (day -14)	12 mm (day 322)	Posterior fibroid, possible endometrial hyperplasia
	3 mm (day -19)	5 mm (day 361)	2 small fibroids
	3 mm (day -20)	4 mm (day 375)	2 small fibroids
	2.5 mm (day -19)	12 mm (day 361)	None
	2.21 mm (day -42)	4 mm (day 362)	None
	1 mm (day -12)	4.8 mm (day 399)	2 small fibroids
	1.7 mm (day -48)	8 mm (day 380)	None
	3.2 mm (day -13)	4.1 mm (day 368)	None
	2.6 mm (day -18)	4.6 mm (day 361)	None
	1.7 mm (day -35)	6.8 mm (day 364)	None
	1.7 mm (day-119)	4.3 mm (day 365)	None
	3 mm (day -21)	7.0 mm (day 379)	None
	1 mm (day -28)	4 mm (day 360)	None
	3.11 mm (day -21)	4.66 mm (day 13)	None
	4 mm (day -39)	5.3 mm (day 369)	8 mm cyst right ovary
	3.6 mm (day -35)	5.5 mm (day 365)	None
	2 mm (day -20)	4 mm (351)	None
	2 mm (day -20)	10 mm (day 78)	None
	1 mm (day -27)	4 mm (day 289)	None

Subjects treated with placebo vaginal tablet:

Subject ID	Baseline TVU	End-of-Study TVU	Other Findings
(b)(6)	3.5 mm (day -24)	4.43 mm (day 379)	Old fibroids and calcifications noted
	2.21 mm (day -56)	5.43 mm (day 367)	None
	1.2 mm (day -23)	9 mm (day 352)	None

(b)(6)	3.7 mm (day -30)	6.8 mm (day 365)	None

A total of 9 subjects had a TVU double-wall endometrial thickness ≥ 4 mm at week 52 or at early termination in Study VAG-1748. The following presentation demonstrates the TVU information available for these 9 subjects.

Subject ID	Screening TVU	End-of-Study TVU	Other Findings
(b)(6)	1.6 mm (day -19)	4.2 mm (day 365)	None
	3.8 mm (day -15)	4.0 mm (day 360)	None
	3.3 mm (day -21)	5.1 mm (day 358)	None
	3.9 mm (day -21)	5.0 mm (day358)	None
	3.8 mm (day -11)	4.0 mm (day371)	None
	3.1 mm (day -54)	6.0 mm (day 374	Uterine myoma
	3.2 mm (day -21)	5.8 mm (day 373)	None
	3.3 mm (day -21)	4.7 mm (day 373)	None
	3.8 mm (day -22)	5.2 mm (day 322)	None

Medical Officer's Comments:

From the reported TVU findings at week 52 (or early termination) in Study VAG-2195, 10.2% of subjects (21 of 205 treated subjects) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study TVU ≥ 4 mm compared to 3.8% of subjects (4 of 103 treated subjects) in the placebo vaginal tablet treatment group.

From the reported TVU findings at week 52 (or early termination) in Study VAG-1748, 2.6 % of subjects (9 of 336 treated subjects) had an end-of-study TVU ≥ 4 mm.

Overall, these findings reflect the known effect of unopposed estrogen stimulation of the endometrium, and do not raise any safety concerns. The lower incidence of subjects reported to have an end-of-study TVU ≥ 4 mm in Study VAG-1748 (2.6%) versus the higher incidence of subjects reported to have an end-of-study TVU ≥ 4 mm in Study VAG-2195 (10.2%) is unexplained.

Endometrial Biopsy:

In Study VAG-2195, all subjects had a uterus and had an endometrial biopsy performed at screening and at the end-of-study or early termination provided the subjects had been treated for 3 months or longer. Subjects with endometrial hyperplasia or cancer at screening were excluded from the study. Transvaginal ultrasound (TVU) assessments were conducted preceding the endometrial biopsy. An evaluable endometrial biopsy at screening was defined as "endometrial tissue sufficient for diagnosis". Per the study protocol, if no tissue was obtained at screening the biopsy could be repeated. Endometrial biopsies with insufficient tissue for diagnosis and TVU double-wall thickness < 4 mm could be categorized as "atrophic endometrium".

Endometrial tissue obtained was "processed in the same manner by a central laboratory". Two independent pathologists blinded to treatment and time of biopsy assessed each endometrial sample. In case of disagreement between the two pathologists, a third blinded pathologist adjudicated the final histologic determination. The Agency's 2003 draft clinical evaluation guidance document recommended histologic characteristics of the endometrium were followed.

One hundred and seventy-two subjects (84%, 172 of 205 treated subjects) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study endometrial biopsy performed in Study VAG-2195. Seventy-nine subjects (77%, 79 of 103 treated subjects) in the placebo vaginal tablet treatment group had end-of-study endometrial biopsies performed. The results of the screening and end-of-study endometrial biopsies are shown in Table 5.

Table 5: Endometrial Biopsy Results in Study VAG-2195

	10 mcg Estradiol Vaginal Tablet	**Placebo Vaginal Tablet**	**Total**
Subjects with endometrial biopsy, n (%)			
Screening	201 (98.0)	102 (99.0)	303 (98.4)
Week 52[a]	172 (83.9)	79 (76.7)	251 (81.5)
Histology of the endometrium, n (%)[b]			
No tissue			
Screening	19 (9.5)	10 (9.8)	29 (9.6)
Week 52	31 (18.0)	18 (22.8)	49 (19.5)
Tissue insufficient for diagnosis			
Screening	40 (19.9)	26 (25.5)	66 (21.8)
Week 52	42 (24.4)	19 (24.1)	61 (24.3)
Atrophic			
Screening	112 (55.7)	54 (52.9)	166 (54.8)
Week 52	66 (38.4)	32 (40.5)	98 (39.0)
Inactive			
Screening	23 (11.4)	9 (8.8)	32 (10.6)
Week 52	26 (15.1)	10 (12.7)	36 (14.3)
Proliferative			
Screening	0	0	0
Week 52	0	0	0
Secretory			
Screening	0	0	0
Week 52	0	0	0
Menstrual type			
Screening	0	0	0
Week 52	0	0	0
Simple hyperplasia without atypia			
Screening	0	0	0
Week 52	0	0	0
Simple hyperplasia with atypia			
Screening	0	0	0
Week 52	0	0	0
Complex hyperplasia without atypia			
Screening	0	0	0
Week 52	1 (0.5)[c]	0	1 (0.4)
Complex hyperplasia with atypia			

	10 mcg Estradiol Vaginal Tablet	Placebo Vaginal Tablet	Total
Screening	0	0	0
Week 52	0	0	0
Carcinoma			
Screening	0	0	0
Week 52	1 (0.6)	0	1 (0.4)
Polyps			
Screening	6 (3.0)	3 (2.9)	9 (3.0)
Week 52	3 (1.2)	0	3 (1.2)
Other			
Screening	1 (0.5)	0	1 (0.3)
Week 52	2 (1.2)	0	2 (0.8)

Source: Adapted from sNDA 20-908/SE1-013, Final Clinical Study Report, Table 12-7, page 86 of 1507.

a. All week 52 values presented are week 52 or last observation carried forward (LOCF).
b. The percentages for each category of the "Histology of the endometrium" are based on the number of subjects with endometrial biopsy at screening and week 52, respectively.
c. Patient reported to have received study medication for 9 days.

Medical Officer's Comments:

In Study VAG-2195, 81.5% (251 of 308 treated subjects) had endometrial biopsies performed at end-of-study (week 52 or early termination). One hundred seventy-two (172) of these subjects were in the 10 mcg estradiol vaginal tablet treatment group and 79 subjects were in the placebo vaginal tablet treatment group. As shown in Table 5, the majority of reported outcomes include diagnoses reported as tissue insufficient for diagnoses, atrophic, and inactive. These findings are considered within normal histological limits. No assessment of the endometrium can be rendered, however, if the biopsy specimen contains no endometrial tissue.

In Study VAG-2195, 36% of the subjects in both treatment groups (73 of 205 treated subjects in the 10 mcg estradiol vaginal tablet treatment group and 37 of 103 treated subjects in the placebo vaginal tablet treatment group) had either no endometrial tissue present in the biopsy specimen or endometrial tissue insufficient for diagnosis. A comparison with reported end-of-study TVU results fortunately showed that the majority of these subjects had TVUs reported as < 4 mm. An endometrial biopsy result reported as endometrial tissue insufficient for diagnosis and a TVU < 4 mm is accepted to represent an endometrium without evidence of endometrial hyperplasia provided a valid attempt has been made to sample the endometrium. Such is not the case, however, for an end-of study endometrial biopsy reported as no tissue with a TVU of ≥ 4. The following subjects were reported to have end-of-study endometrial biopsies reported as no tissue or tissue insufficient for diagnosis and a TVU of 4 mm of greater:

10 mcg estradiol vaginal tablet treatment group:

- *Subject* (b)(6) *with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 361) had a TVU reported as 12 mm (day 361)*
- *Subject* (b)(6) *with a diagnosis of tissue insufficient for diagnosis at end-of-study (day 399) had a TVU reported as 4.8 mm (day 399)*

- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 364) had a TVU reported as 6.8 mm (day 364)*
- *Subject (b)(6) with a diagnosis of no tissue on endometrial biopsy at end-of-study (day 365) had a TVU reported as 4.3 mm (day 365)*
- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 360) had a TVU reported as 4 mm (day 360)*

Placebo vaginal tablet treatment group:

- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 379) had a TVU reported as 4.43 mm (day 379)*
- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 367) had a TVU reported as 5.43 mm (day 367)*

The Applicant provided follow-up information for two subjects of particular interest: Subject (b)(6) and Subject (b)(6). Per the follow-up information provided, a recording error was made on the Case Report Form for Subject (b)(6) A site monitor recorded the endometrial thickness as 12 mm. The end-of-study TVU report, obtained on (b)(6), indicated an endometrial thickness of 1.2 mm. Follow-up information provided for Subject (b)(6) indicates that Subject (b)(6) "has received annual gynecologic care and routine medical care since the end of study visit on (b)(6). She denied any vaginal bleeding and has been offered free of charge follow-up vaginal ultrasound and/or endometrial biopsy which she refused." Therefore, no final outcome is available for Subject (b)(6).

Table 5 also demonstrates that no subjects in the placebo vaginal tablet treatment group were diagnosed with abnormal endometrial findings including polyps, endometrial hyperplasia or endometrial cancer in 52-week Study VAG-2195. See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of the seven abnormal findings reported in Study VAG-2195 for the 10 mcg estradiol vaginal tablet treatment group.

Endometrial biopsies were not performed in 12-week Study VAG-1850.

Medical Officer's Comments:

The finding of 1 case of endometrial cancer in a 52-week clinical trial of unopposed estrogen use in postmenopausal women with uteri is not unexpected. Subject (b)(6) presented with vaginal bleeding on day 322 and was diagnosed with endometrial cancer on day 326. Estrogen class labeling advises patients and healthcare providers of the need for close clinical surveillance, including adequate measures in all cases of unusual vaginal bleeding. The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus.

One case of endometrial hyperplasia without atypia was also reported in Study VAG-2195. Subject (b)(6) had an endometrial biopsy performed on day -37 which was reported as polyps, atrophic type. An endometrial biopsy obtained on study day 43 was reported as complex

hyperplasia without atypia. Subject (b)(6) *reportedly took only 9 days of study medication. No complaints of vaginal spotting/bleeding were recorded for this subject.*

The endometrial findings reported in Phase 3a Study VAG-2195 (one case each of endometrial cancer and complex hyperplasia without atypia) support the use of estrogen class labeling for the 10 mcg estradiol vaginal tablet.

All subjects in Study VAG-1748 had a uterus and had an endometrial biopsy performed at screening and at the end-of-study or early termination provided the subjects had been treated for 3 months or longer. Subjects with endometrial hyperplasia or cancer at screening were excluded from the study. Transvaginal ultrasound (TVU) assessments were conducted preceding the endometrial biopsy. An evaluable endometrial biopsy at screening was defined as "endometrial tissue sufficient for diagnosis". Per the study protocol, if no tissue was obtained at screening the biopsy could be repeated. Endometrial biopsies with insufficient tissue for diagnosis and TVU double-wall thickness < 4 mm could be categorized as "atrophic endometrium".

Endometrial tissue obtained by Pipelle was submitted to (b)(4) (b)(4). Two independent pathologists blinded to treatment and time of biopsy assessed each endometrial sample. In case of disagreement between the two pathologists, a third blinded pathologist adjudicated the final histologic determination. The Agency's 2003 draft clinical evaluation guidance document recommended histologic characteristics of the endometrium were followed.

A total of 336 subjects in Study VAG-1748 had a baseline endometrial biopsy performed, and a total of 297 subjects (88.4%, 297 of 336 subjects) had an end-of treatment endometrial biopsy performed (including premature discontinuations and week 52 completers). The results of the screening and end-of-treatment endometrial biopsies are shown in Table 6.

Table 6: Endometrial Biopsy Results in Study VAG-1748

Time Period and Histology of the Endometrium	**10 mcg Estradiol Vaginal Tablet N = 336**
Subjects with endometrial biopsy, n (%)	
Screening	336 (100.0)
Week 52	284 (84.5)[a]
Week 52 (LOCF)	297 (88.4)
Histology of the endometrium, n (%)	
No tissue	
Screening	4 (1.2)
Week 52	21 (7.4)
Week 52 (LOCF)	22 (7.4)
Tissue insufficient for diagnosis	
Screening	129 (38.4)
Week 52	85 (29.9)
Week 52 (LOCF)	89 (30.0)
Atrophic	
Screening	161 (47.9)
Week 52	136 (47.9)
Week 52 (LOCF)	143 (48.1)

Time Period and Histology of the Endometrium	10 mcg Estradiol Vaginal Tablet N = 336
Inactive	
Screening	35 (10.4)
Week 52	39 (13.7)
Week 52 (LOCF)	40 (13.5)
Weakly Proliferative	
Screening	2 (0.6)
Week 52	1 (0.4)
Week 52 (LOCF)	1 (0.3)
Disordered Proliferative	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Secretory	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Menstrual type	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Simple hyperplasia without atypia	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Simple hyperplasia with atypia	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Complex hyperplasia without atypia	
Screening	0
Week 52	0[b]
Week 52 (LOCF)	0
Complex hyperplasia with atypia	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Carcinoma	
Screening	0
Week 52	0
Week 52 (LOCF)	0
Polyps	
Screening	3 (0.9)
Week 52	2 (0.7)
Week 52 (LOCF)	2 (0.7)
Other	
Screening	2 (0.6)
Week 52	0
Week 52 (LOCF)	0

Source: Adapted from sNDA 20-908/SE1-013 re-submission, Final Clinical Study Report, Table 12-8, page 65 of 840.

[a] Subject (b)(6) withdrew at a late stage but had a biopsy result at week 52. Therefore, the number of biopsies at week 52 is 284 although only 283 subjects completed Study VAG-1748.
[b] This reviewer believes that one case of "complex hyperplasia without atypia" was identified at end of treatment for Subject (b)(6) (see discussion that follows).
Definition: LOCF = last observation carried forward.

Medical Officer's Comments:

In Study VAG-1748, 88.4% (297 of 336 treated subjects) had endometrial biopsies performed at end-of study (week 52 or early termination). As shown in Table 6, the majority of reported outcomes include diagnoses reported as tissues insufficient for diagnoses, atrophic, inactive, and weakly proliferative. These categories of endometrial biopsy outcomes are considered within normal histological limits. No assessment of the endometrium can be rendered, however, if the biopsy specimen contains no endometrial tissue (7.4%, 22 subjects at week 52 [LOCF]).

In Study VAG-1748, one subject (Subject (b)(6)) was reported to have an end-of-study (day 358) endometrial biopsy reported as tissue insufficient for diagnosis and a TVU reported as 5.1 mm. All other subjects shown in Table 6 as having no endometrial tissue or endometrial tissue insufficient for diagnosis at week 52 and week 52 (LOCF) had TVUs reported as < 4 mm. An endometrial biopsy result reported as no tissue or endometrial tissue insufficient for diagnosis and a TVU < 4 mm is accepted to represent an endometrium without evidence of endometrial hyperplasia provided a valid attempt has been made to sample the endometrium.

Per the Applicant-reported results demonstrated in Table 6, there were no confirmed cases of endometrial hyperplasia or carcinomas reported in 52-week Study VAG-1748. The Applicant indicates, however, that "there was one false positive result of endometrial hyperplasia". The one reported "false positive" abnormal findings reported in Study VAG-1748 for the 10 mcg estradiol vaginal tablet treatment group is summarized below:

Subject (b)(6) (Norway):

The screening double wall TVU obtained on study day -16 (b)(6)) was reported as 2.0 mm. The screening endometrial biopsy obtained on study day -16 (b)(6)) was reported as follows:

Pathologist 1 = Unsatisfactory for diagnosis; limited surface endometrium present
Pathologist 2 = Unsatisfactory for diagnosis; limited surface endometrium present

Subject (b)(6) did not report any vaginal spotting or bleeding during treatment. The end-of-study double wall TVU obtained on study day 364 (b)(6)) was reported as 2.0 mm. The end-of-study endometrial biopsy also obtained on study day 364 (b)(6)) was reported as follows:

Pathologist 1 = Tissue volume too scant for diagnosis – no endometrium present, normal ectocervical and endocervical tissue
Pathologist 2 = Unsatisfactory for diagnosis: limited surface endometrium present

A repeat endometrial biopsy was performed on [redacted] *(day 391) per the protocol:*

Pathologist 1 = Endometrial hyperplasia, complex type (no atypia), epithelial metaplasia, mucinous type
Pathologist 2 = Polyp, hyperplastic type, epithelial metaplasia, papillary mucinous type (no atypia)
Pathologist 3 = Endometrial hyperplasia, complex type (no atypia)

A fractionated abrasion was performed on [redacted] *at the* [redacted] *in Norway. A translated report indicates the following:*

Fractionated abrasion performed under general anesthesia, womb palpated mobile normal size, cervix stretched to Hegar 8, sharp curette until good wall contact, probe size 7 cm, very little material. The histology report indicates:

1. "endocerv. epithelium without evidence of atypical cells"
2. "ex mucous membrane without evidence of atypical cells. No evidence of endometrium."

Per the "Investigator's statement" provided, "I hereby certify that, based on all assessments as described above, the diagnosis of "endometrial hyperplasia, complex type (without atypia)" for study subject no. [redacted] *has not been confirmed. This diagnosis as per the* [redacted] *biopsy report dated* [redacted] *is to be considered a false positive diagnosis. The clinical assessment, the first biopsy result, measurement of endometrial thickness as per TVU and the result and histological examination of the fractionated abrasion lead to the conclusion that subject* [redacted] *should have a diagnosis of "atrophic endometrium" as a final study outcome."*

The reviewer disagrees with the conclusion regarding Subject [redacted] provided in the May 26, 2009 re-submission. Two out of three blinded pathologists reported complex hyperplasia without atypia on the repeat endometrial biopsy specimen. The absence of histologic evidence following uterine dilatation and curettage does not negate the reported endometrial biopsy findings. In addition, the DRUP safety review team (consisting of the medical team leader, the primary reviewer, and a second reviewer who is a board-certified gynecologic pathologist) also disagrees with the Applicant's conclusion regarding Subject [redacted].

The finding of one case of endometrial hyperplasia, complex type (without atypia) in 52-week Study VAG-1748 is not unexpected. Estrogen class labeling advises patients and healthcare providers of the need for close clinical surveillance when unopposed estrogen is given to a postmenopausal woman with a uterus. The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus.

Medical Officer's Comments:

The endometrial findings reported in Study VAG-2195 and Study VAG-1748 (1 case of endometrial cancer and 2 cases of complex hyperplasia without atypia) support the use of estrogen class labeling for the 10 mcg estradiol vaginal tablet.

Vaginal Bleeding:

In total, 12 subjects reported vaginal bleeding in Study VAG-2195 (9 in the 10 mcg estradiol vaginal tablet treatment group [4.4%, 9 of 205 treated subjects] and 3 subjects in the placebo vaginal tablet treatment group [3.0%, 3 of 103 treated subjects]). Only 1 of these 9 subjects discontinued due to the adverse event (Subject (b)(6) in the 10 mcg estradiol vaginal tablet treatment group).

Four subjects in 52-week Study VAG-1748 reported vaginal bleeding (1.2%, 4 of 336 treated subjects). No subject discontinued due to the adverse event.

Medical Officer's Comments:

Overall, the percentage of women reporting vaginal bleeding was low in 52-week Studies VAG-2195 and VAG-1748. In Study VAG-2195, similarity is noted between the active and placebo treatment groups in the percentage of women reporting vaginal bleeding (4.4% in the 10 mcg estradiol vaginal tablet treatment group versus 3.0% in the placebo vaginal tablet treatment group).

7.1.4 Other Search Strategies

No algorithm involving combination of clinical findings and a marker for a particular toxicity was developed with the exception of the interrelationship between the use of unopposed estrogen in a woman with a uterus and the finding of endometrial thickness and endometrial hyperplasia/cancer as discussed in Subsection 7.1.3.3, "Other significant adverse events".

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Safety is summarized for all randomized subjects who applied at least 1 dose of study medication. Two hundred and five (205) subjects made up the safety population of women who received the 10 mcg estradiol vaginal tablet in 52-week Study VAG-2195. Fifty-seven (57) subjects made up the safety population in 12-week Study VAG-1850. Three hundred and thirty-six (336) subjects make up the safety population in Study VAG-1748. All enrolled subjects received 10 mcg estradiol vaginal tablets in Study VAG-1748.

Safety was evaluated from the results of subject reported signs and symptoms, history reported by the subject, vital sign measurements, scheduled physical examinations, and diagnostic assessments performed including mammograms, Pap smears, TVUs, and endometrial biopsies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Per the submission, all reported adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0. Pre-existing conditions found as a result of screening procedures were not reported as adverse events. Treatment-emergent adverse events (TEAE) were defined as: 1) Events reported during the clinical trial that were not present before treatment with study medication; or 2) Events that were present prior to treatment which worsened during the clinical trial. Adverse events and TEAEs were summarized by body system and treatment group.

7.1.5.3 Incidence of common adverse events

In Phase 3a, 52-week Study VAG-2195, 235 subjects (76.3%) experienced a least one TEAE (158 of 205 treated subjects [77%] in the 10 mcg estradiol vaginal tablet treatment group and 77 of 103 treated subjects [75%] in the placebo vaginal tablet treatment group). The most commonly reported adverse events in the 10 mcg estradiol vaginal tablet treatment group were vulvovaginal mycotic infection (8.3%, 17 of 205 treated subjects), vulvovaginal pruritis (7.8%, 16 of 205 treated subjects), and headache (7.3%, 15 of 205 treated subjects). The most commonly reported adverse events in the placebo vaginal tablet treatment group were headache (12.6%, 13 of 103 treated subjects), vulvovaginal discharge (7.8%, 8 of 103 treated subjects), and nasopharyngitis (6.8%, 7 of 103 treated subjects).

In Phase 1, 12-week Study VAG-1850, 48 subjects (84.2%) experienced at least one TEAE (23 of 29 subjects [79.3%] in the 10 mcg estradiol vaginal tablet treatment group and 25 of 28 treated subjects [89.3%] in the Vagifem® 25 mcg treatment group). The most commonly reported adverse events in the 10 mcg estradiol vaginal tablet treatment group were headache (27.6%, 8 of 29 treated subjects), vaginal discharge (13.8%, 4 of 29 treated subjects), nasopharyngitis (13.8%, 4 of 29 treated subjects), and nausea (13.8%, 4 of 29 treated subjects). The most commonly reported adverse events in the Vagifem® 25 mcg treatment group were headache (32.1%, 9 of 28 treated subjects), diarrhea (17.9%, 5 of 28 treated subjects), nasopharyngitis (17.9%, 5 of 28 treated subjects), and vaginal discharge (14.3%, 4 of 28 treated subjects).

See Tables 7 and 8 for more information on common adverse events in these two clinical trials. Tables 7 and 8 are sorted by decreasing frequency in the 10 mcg estradiol vaginal tablet treatment group.

In non-IND Study VAG-1748, 186 (55.4%, 186 of 336 treated subjects) reported treatment emergent adverse events. The most commonly reported adverse events were nasopharyngitis

(5.1%, 17 of 336 treated subjects), headache (4.8%, 16 of 336 treated subjects), urinary tract infection (3.6%, 12 of 336 treated subjects), and back pain (2.7%, 9 of 336 treated subjects). See Table 9 for more information on common adverse events in this clinical trial. Table 9 is sorted by decreasing frequency.

7.1.5.4 Common adverse event tables

Table 7: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for ≥ 5% in Any Treatment Group in 12-Month Study VAG-2195

Study VAG-2195	**10 mcg Estradiol Vaginal Tablet (N=205) n (%)**	**Placebo Vaginal Tablet (N=103) n (%)**	**Total (N=308) n (%)**
Vulvovaginal mycotic infection	17 (8.3)	3 (2.9)	20 (6.5)
Vulvovaginal pruritis	16 (7.8)	2 (1.9)	18 (5.8)
Headache	15 (7.3)	13 (12.6)	28 (9.1)
Nasopharyngitis	14 (6.8)	7 (6.8)	21 (6.8)
Back pain	14 (6.8)	2 (1.9)	16 (5.2)
Vaginal discharge	12 (5.9)	8 (7.8)	20 (6.5)
Diarrhea	11 (5.4)	0 (0.0)	11 (3.6)

Source: Adapted from sNDA 20-908SE1-013, Summary of Clinical Safety Studies, Table 2-1 on page 12 of 46 and Table 2-5 on page 19 of 46.

Table 8: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for ≥ 5% in Any Treatment Group in 12-Week Study VAG-1850

Study VAG-1850	**10 mcg Estradiol Vaginal Tablet (N=29) n (%)**	**Vagifem® 25 mcg (N=28) n (%)**	**Total (N=57) n (%)**
Headache	8 (27.6)	9 (32.1)	17 (29.8)
Diarrhea	3 (10.3)	5 (17.9)	8 (14.0)
Nasopharyngitis	4 (13.8)	5 (17.9)	9 (15.8)
Vaginal discharge	4 (13.8)	3 (14.3)	8 (14.0)
Nausea	4 (13.8)	1 (3.6)	5 (8.8)
Weight increase	3 (10.3)	3 (10.7)	6 (10.5)
Pharyngolaryngeal pain	3 (10.3)	1 (3.6)	4 (7.0)
Peripheral edema	3 (10.3)	1 (3.6)	4 (7.0)
Back pain	2 (6.9)	4 (14.3)	6 (10.5)
Metrorrhagia	2 (6.9)	3 (10.7)	5 (8.8)
Vomiting	2 (6.9)	2 (7.1)	4 (7.0)
Pain in extremity	2 (6.9)	1 (3.6)	3 (5.3)
Hot flush	2 (6.9)	1 (3.6)	3 (5.3)
Hematoma	2 (6.9)	-	2 (3.5)
Phlebitis	2 (6.9)	-	2 (3.5)
Flatulence	1 (3.4)	4 (14.3)	5 (8.8)
Cough	1 (3.4)	2 (7.1)	3 (5.3)
Malaise	-	2 (7.1)	2 (3.5)
Fall	-	2 (7.1)	2 (3.5)
Bronchitis	-	2 (7.1)	2 (3.5)
Dizziness	-	2 (7.1)	2 (3.5)

Source: Adapted from sNDA 20-908SE1-013, Summary of Clinical Safety Studies, Table 2-1 on page 12 of 46 and Table 2-5 on page 19 of 46.

Table 9: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for ≥ 1% of Subjects in 12-Month Study VAG-1748[a]

Preferred Term	**10 mcg Estradiol Vaginal Tablet (N = 336) n (%)**
Nasopharyngitis	17 (5.1)
Headache	16 (4.8)
Urinary tract infection	12 (2.7)
Back pain	9 (2.7)
Pain in extremity	7 (2.1)
Abdominal pain	7 (2.1)
Sinusitis	7 (2.1)
Arthralgia	7 (2.1)
Vulvovaginal discomfort	7 (2.1)
Hot flush	6 (1.8)
Hypertension	6 (1.8)
Vaginal discharge	6 (1.8)
Vulvovaginal candidiasis	6 (1.8)
Cystitis	5 (1.5)
Osteoarthritis	5 (1.5)
Pollakiuria	5 (1.5)
Vulvovaginal pruritis	5 (1.5)
Cough	5 (1.5)
Abdominal pain upper	5 (1.5)
Diarrhea	4 (1.2)
Toothache	4 (1.2)
Basal cell carcinoma	4 (1.2)
Vaginal hemorrhage	4 (1.2)

Source: Adapted from sNDA 20-908/SE1-013 re-submission dated May 26, 2009, Table 12-4, page 50 of 840.
[a] Treatment Emergent Adverse Event is defined as an event between the first- and last dose dates + 30 days or starting before the first dose with increasing severity during the period.

Medical Officer's Comments:

The common reported treatment-emergent adverse events in Study VAG-2195, Study VAG-1850, and Study VAG-1748 are not unknown with vaginal estrogen-alone therapy. The adverse events demonstrated in Tables 7 and 8 and Table 9 do not raise safety issues for the 10 mcg estradiol vaginal tablet product.

7.1.5.5 Identifying common and drug-related adverse events

In Study VAG-2195, a larger percentage of subjects in the 10 mcg estradiol vaginal tablet treatment group reported vulvovaginal mycotic infection/pruritis, back pain and diarrhea as compared with the placebo treatment group. Headache and vaginal discharge were reported in both treatment groups in Study VAG-2195, however, a higher incidence of these events were reported in the placebo vaginal tablet treatment group.

Overall, subjects randomized to the Vagifem® 25 mcg treatment group in Study VAG-1850 reported a higher incidence of common adverse events with the exceptions noted in Table 8.

Similarities are noted in Study VAG-2195 and Study VAG-1748 for the 10 mcg estradiol vaginal tablet treatment group. Both studies reported vulvovaginal mycotic infection, vulvovaginal pruritis, and vaginal discharge.

7.1.5.6 Additional analyses and exploration

No additional analyses were performed on the reported most common treatment-emergent adverse events.

7.1.6 Less Common Adverse Events

See the discussion regarding the reported endometrial findings in Subsection 7.1.3.3 "Other significant adverse events".

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory assessments of hematology (hemoglobin, hematocrit, red blood cell count [RBC], white blood cell count [WBC], platelet count), biochemistry (total bilirubin, alkaline phosphatase [AP], gamma glutamyltransferase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine), and sex hormones (estradiol, estrone, estrone sulfate, sex hormone-binding globulin [SHBG], FSH, LH) were performed at baseline and end-of-study in Study VAG-2195.

Clinical laboratory assessments of hematology (hemoglobin, hematocrit, RBC, WBC, platelet count, mean corpuscular volume [MCV], partial thromboplastin time [a=PTT]), biochemistry (ALT, AST, GGT, total bilirubin, creatinine, potassium, glucose) and urinalysis (pH, glucose, blood, protein) were performed at the screening, baseline and end-of-study visits in Study VAG-1850. In addition, in this study, samples for the pharmacokinetic profiles for estradiol, estrone, and estrone sulfate in plasma were also obtained on days -1, 1-2, 14-15, 82-83 and 1 sample each on days 7, 30 and 58.

Clinical laboratory assessments of hematology (hemoglobin, hematocrit, RBC, WBC, platelet count), biochemistry (total bilirubin, AP, GGT, AST, ALT, and creatinine), and sex hormones (estradiol and FSH) were performed at baseline and end-of-study in Study VAG-1748.

Medical Officer's Comments:

The laboratory assessments obtained during the conduct of these three studies appear appropriate and adequate.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

In 52-week Study VAG-2195, 12-week Study VAG-1850, and 52-week Study VAG-1748, laboratory assessments were performed at screening and end-of-study (or early termination). Clinically relevant differences, for the assessments performed, from normal reference ranges and from individual subject screening values in all treatment groups were reported in the December 7, 2007 submission and in the May 26, 2009 re-submission.

7.1.7.3 Standard analyses and explorations of laboratory data

See the information provided in Subsection 7.1.7.1 "Overview of laboratory testing in the development program". In the December 7, 2007 submission and the May 26, 2009 re-submission, clinically relevant differences, for the assessments performed, from normal reference ranges and from individual subject screening values in all treatment groups were reported.

In Study VAG-2195, there were no clinically relevant differences from normal reference ranges or from screening values for any of the laboratory assessments performed for either the 10 mcg estradiol vaginal tablet treatment group or the placebo vaginal tablet treatment group. Individual subject changes were evaluated through shift tables and showed no clinically significant abnormalities. Similar findings are reported in Study VAG-1850 with one exception. Subject (b)(6) was observed to have a major laboratory deviation of clinical relevance during screening (GTT value of 290U/L). Subject (b)(6) was withdrawn from Study VAG-1850 before study drug administration.

In Study VAG-1748, the mean values for the hematology, biochemistry, and sex hormone parameters remained within the normal range at baseline and end-of-study. However, a total of 13 subjects experienced 17 laboratory abnormalities reported as treatment-emergent adverse events. See Table 10.

Table 10: Laboratory-Related Treatment Emergent Adverse Events in Study VAG-1748

System Organ Class **Preferred Term**	**10 mcg Estradiol Vaginal Tablet** **(N = 336)** **n (%)**
Investigations	8 (2.4)
Alanine aminotransferase increased	2 (0.6)
Aspartate aminotransferase increased	2 (0.6)
Blood cholesterol increased	2 (0.6)
Gamma-glutamyl transferase increased	2 (0.6)
Metabolism and nutrition disorders	5 (1.5)
Hypercholesterolemia	2 (0.6)
Hyperlipidemia	1 (0.3)
Hypokalemia	1 (0.3)
Vitamin B 12 deficiency	1 (0.3)

Source: Adapted from sNDA 20-908/SE1-013 re-submission dated May 26, 2009, Table 12-6, page 61 of 840.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations of laboratory data were performed.

7.1.7.5 Special assessments

See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of the sex hormone levels reported in Study VAG-2195 and Study VAG-1850.

In Study VAG-1748, estradiol and FSH were analyzed and the changes in these sex hormones from screening to end-of-study are shown in Table 11.

Table 11: Sex Hormone Analysis in Study VAG-1748

Sex Hormone	**Observed Data**			**Change from Screening**		
Visit	N	Mean	SD	N	Mean	SD
Estradiol						
Screening	336	5.15	0.96	-	-	-
Week 52/ EOT	309	6.05	8.69	309	0.88	8.70
FSH						
Screening	336	77.62	24.2	-	-	-
Week 52/ EOT	311	73.24	22.5	311	-4.31	11.06

Source: Adapted from sNDA 20-908/SE1-013 resubmission, Table 14.3.6-7, pages 166 and 167 of 840.

Medical Officer's Comments:

There were no clinically relevant changes from normal reference ranges or from screening values at week 52 in Study VAG-1748.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the December 7, 2007 submission, the safety population included all randomized subjects who received at least 1 dose of study medication. During the 52-week Study VAG-2195, 308 subjects were included in the safety population (205 subjects in the 10 mcg estradiol vaginal tablet treatment group and 103 subjects in the placebo vaginal tablet treatment group). During the 12-week Study VAG-1850, 57 subjects were included in the safety population (29 subjects in the 10 mcg estradiol vaginal tablet treatment group and 28 subjects in the Vagifem® 25 mcg treatment group).

In the May 26, 2009 re-submission, the safety population for 52-week Study VAG-1748 also included all randomized subjects who received 1 dose of study medication (all 336 subjects received 10 mcg estradiol vaginal tablets).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

In this submission, the safety population included all randomized subjects who received at least 1 dose of study medication.

7.1.8.3 Standard analyses and explorations of vital signs data

There were no clinically relevant changes in any of the vital sign parameters (systolic and diastolic blood pressure and pulse) and weight for subjects in Study VAG-2195 and Study VAG-1748. Subjec (b)(6) in Study VAG-1850 in the 10 mcg estradiol vaginal tablet treatment group developed hypertensive values and was referred to her primary care practitioner who started her on antihypertensive treatment with beta blocker after day 58 of study participation. Subject (b)(6) completed Study VAG-1850. No additional analysis of vital signs data was performed by the reviewer.

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data was performed by the reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were not obtained Study VAG-2195 or in Study VAG-1748.

During the conduct of Study VAG-1850, Subject (b) (6) in the Vagifem® 25 mcg treatment group was found to have an asymptomatic cardiac arrhythmia during visit 5 (week 8). A cardiologic examination including a long term ECG showed a cardiac arrhythmia with intermittent atrial fibrillation and ventricular extra systoles. Treatment with a beta blocker was started. Subject (b) (6) completed Study VAG-1850.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and exploration of ECG data were performed or conducted.

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

No QT or QT_c interval data was included in the December 7, 2007 submission or in the May 26, 2009 re-submission. No cases of Torsades de pointes or ventricular tachycardia were reported in the safety data.

7.1.10 Immunogenicity

No human immunogenicity studies, data, or published literature were submitted with the sNDA.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under IND (b)(4) for 10 mcg estradiol vaginal tablets. No data or published literature was submitted with the sNDA on human carcinogenicity.

Currently, the Agency recommends that the following information be included in estrogen class labeling: "Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver."

7.1.12 Special Safety Studies

No special safety studies were conducted during the drug development program for 10 mcg estradiol vaginal tablets.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Per the December 7, 2007 submission and the May 26, 2009 re-submission, there were no cases of overdose with the study medication in the clinical development program of 10 mcg estradiol vaginal tablets.

7.1.14 Human Reproduction and Pregnancy Data

Given that the indication being sought in sNDA 20-908/SE1-013 is the (b)(4) (b)(4)", no formal studies in humans on the effects of 10 mcg estradiol vaginal tablets in human reproduction or pregnancy were performed.

7.1.15 Assessment of Effect on Growth

10 mcg estradiol vaginal tablets have not been tested in pediatric subjects.

7.1.16 Overdose Experience

No cases of overdose with 10 mcg estradiol vaginal tablets have been reported during the drug development program.

7.1.17 Postmarketing Experience

Vagifem® (estradiol vaginal tablets) 25 mcg was approved in 1999 for the treatment of atrophic vaginitis.

The Division of Adverse Event Analysis (DAEA) was consulted for a safety review for Vagifem® during the first review cycle. Per the consultation, the term "data mining" refers to the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences (i.e., "signals") in large databases. These signals can then be evaluated for intervention as appropriate. The WebVDME data mining application from Lincoln Technologies was searched on February 14, 2008 using the trade name "Vagifem". In addition, the Adverse Event Reporting System (AERS) was searched. AERS "s a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. FDA receives adverse drug reaction reports from manufacturers as required by regulation, including foreign and domestic reports. Health care professionals and consumers send reports voluntarily through the MedWatch program. Based on data entry rules, the adverse events reports are entered into the AERS database. All reported adverse event terms are coded using a standardized international terminology, MedDRA (Medical Dictionary for Regulatory Activities)."

"A search of the AERS database for any report with the suspect drug Vagifem listed as the Trade name retrieved 188 cases. The commonly reported preferred term (PT) is listed below:

Preferred Term (PT)	**Count of PTs**	**Percent of Total**
Breast Cancer Female	85	45.21%
Breast Cancer	19	10.11%
Pain	14	7.45%
Anxiety	11	5.85%
Estrogen Receptor Assay Positive	6	3.19%
Progesterone Receptor Assay Positive	6	3.19%
Urticaria	6	3.19%
Psychiatric Symptom	5	2.66%
Vaginal Hemorrhage	5	2.66%

These events were compared against the current approved labeling; the only unlabeled events are anxiety and psychiatric symptom."

"The term psychiatric symptom is too non-specific to be meaningful. Eleven reports of anxiety were retrieved, which is not particularly noteworthy because anxiety disorders are the most

common class of psychiatric disorders. Thus, the searches of the AERS database did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling."

Medical Officer's Comments:

The DAEA consult confirmed that a search of the AERS database for Vagifem® 25 mcg did not identify any adverse events for consideration as additions to the proposed labeling. DAEA had no labeling recommendations based on the postmarketing safety review completed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 "Tables of Clinical Studies" in this review summarizes Study VAG-2195 submitted to support the safety and efficacy of the 10 mcg estradiol vaginal tablet. This study contributed an adequate representation for postmenopausal women in support of safety and efficacy.

Study VAG-1748 supports the safety of the 10 mcg estradiol tablet. Phase 1 Study VAG-1850 provided additional safety data.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 "Tables of Clinical Studies" for the clinical trials conducted. This table summarizes the study design and number of subjects in each treatment group.

7.2.1.2 Demographics

See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of the demographic characteristics for the ITT population in Study VAG-2195 and Study VAG-1850. The following table shows the demographic characteristics for the ITT population in Study VAG-1748.

Table 12: Subject Demographic and Baseline Characteristics in Study VAG-1748

Characteristic	**10 mcg Estradiol Vaginal Tablet**
Numbers randomized	
Age (years) Mean (SD) [Range]	59.5 (6.2) [45-84]
Race (n) Asian/White/Unknown	1/296/39*
Weight (kg) Mean (SD) [Range]	66.20 (9.9) [45.0-98.0]
BMI (kg/m^2) Mean (SD) [Range]	24.58 (3.4) [17.4-34.7]
Time Since Last Menses (years) Mean (SD) [Range]	9.4 (5.9) [1-34]

Source: Adapted from SNDA 20-908/SE1-013 re-submission dated May 26, 2009, Table 11-2, page 43 of 840.
* Due to local regulations, data on race and ethnic background was not collected in France (site numbers 300-309).

Medical Officer's Comments:

Overall, the treatment groups in Study VAG-2195, Study VAG-1850, and Study VAG-1748 were similar with respect to demographics and baseline characteristics.

7.2.1.3 Extent of exposure (dose/duration)

A total of 308 subjects received at least 1 dose of study medication and were included in all safety analyses in 52-week Study VAG-2195. In 12-week Study VAG-1850, 56 of the 57 treated subjects completed the study and were included in the safety analysis. See the Medical Officer's Primary Review, dated October 6, 2008, for the descriptive statistics for the extent of exposure in these two studies.

A total of 336 subjects received at least 1 dose of study medication and were included in all safety analyses in 52-week Study VAG-1748. Descriptive statistics for the extent of exposure are presented in Table 13.

Table 13: Duration of Exposure in Study VAG-1748

Duration	**10 mcg Estradiol Vaginal Tablet** **N = 336**
Duration of treatment, days Mean (SD) [Range]	331.6 (92.32)[2-467]
N (%) Subjects Treated: ≤ Week 2 Week 3 – Week 10 Week 13 – Week 26 Week 27 – Week 40 Week 41 – Week 52 > Week 52	 7 (2.1) 16 (4.8) 9 (2.7) 7 (2.1) 183 (54.5) 114 (34.0)

Source: Adapted from sNDA 20-908/SE1-013 resubmission dated May 26, 2009, Table 12-1, page 46 of 840.

Medical Officer's Comments:

The mean duration of treatment is slightly higher in Study VAG-1748 than in Study VAG-2195 for the 10 mcg estradiol vaginal tablet treatment groups (331.6 days in Study VAG-1748 versus 317.7 days in Study VAG-2195). In addition, a larger percentage of subjects received treatment > Week 52 in Study VAG-1748 than in Study VAG-2195 (34%, 114 of 336 treated subjects in Study VAG-1748 and 27%, 56 of 205 treated subjects in Study VAG-2195). Study VAG-1748 allowed a visit window of 14 days, which may have contributed to this finding.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

See the discussion of non-IND Study VAG-1748 in Section 7.1 "Methods and Findings" and in Subsection 7.1.2 "Other Serious Adverse Events".

7.2.2.2 Postmarketing experience

Vagifem® (estradiol vaginal tablets) 25 mcg has been marketed since year 2000. Postmarketing safety information has been provided proactively by Novo Nordisk Inc. through annual report submissions and labeling updates.

7.2.2.3 Literature

The published literature has extensively documented the potential risk and benefits of estrogen and estrogen plus progestin therapy for the treatment of vasomotor symptoms and symptoms of vulvar and vaginal atrophy due to menopause. These publications have raised appropriate safety concerns regarding both dose and duration of hormone therapy for menopausal symptoms. See page 15 for the review of findings of the National Institutes of Health (NIH) Women's Health Initiative (WHI) studies.

7.2.3 Adequacy of Overall Clinical Experience

A total of 308 treated subjects participated in the Phase 3a Study VAG-2195. Fifty-seven treated subjects participated in 12-week Study VAG-1850. Three hundred and thirty-six subjects (336) participated in non-IND Study VAG-1748.

Medical Officer's Comments:

Overall, the total number os subjects participating in 52-week Studies VAG-2195 and VAG-1748 and 12-week Study VAG-1850 provided adequate safety information for the 10 mcg estradiol vaginal tablet.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required for the 10 mcg estradiol vaginal tablet. It is recognized that long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing conducted in Study VAG-2195, Study VAG-1850, and Study VAG-1748 and the efforts to elicit adverse event data, were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See the Medical Officer's Primary Review, dated October 6, 2008, for a summary of the clinical pharmacology for estradiol. See the Clinical Pharmacology and Pharmacokinetics Review, dated July 17, 2008, for a more detailed discussion. The metabolism and excretion of estrogen drug products are sufficiently understood to address in the label potential safety concerns in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions.

In vitro and *in vivo* studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. No further testing for these previously well defined drug interactions with estradiol are required.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The gynecologic safety data submitted in Study VAG-2195 and Study VAG-1748 is generally adequate. The safety data provided by the Applicant is sufficiently adequate for the evaluation of potential adverse events.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data submitted with sNDA 20-908/SE2-013 for the safety cohort of 308 postmenopausal women with uteri in Study VAG-2195 and 336 postmenopausal women with uteri in Study VAG-1748 is adequate. Both studies provided safety data regarding the use of unopposed estrogen in a woman with a uterus over a treatment duration of 12 months.

7.2.9 Additional Submissions, Including Safety Update

See the Medical Officer's Primary Review, dated October 6, 2008, for a detailed discussion of the 4-Month Safety Update submitted on April 3, 2008 in the first review cycle.

The safety update included in this May 26, 2009 re-submission provides the following information:

- "There are no ongoing nonclinical and/or clinical studied/trials of Vagifem 25 or 10 mcg."
- "There are no new safety data from completed studies VAG-2195 and VAG-1850 since the 120 Day Safety update submitted on April 3, 2008."

On May 28, 2009, the Applicant submitted a Periodic Safety Update Report (PSUR) for the period April 1, 2008 to March 31, 2009 including international PSUR and U.S. specific information for Vagifem® 25 mcg.

Vagifem® 25 mcg is approved in 75 countries. In the reporting period, a total of 258 adverse reaction reports were received for Vagifem® 25 mcg. Approximately (b)(4) of Vagifem® 25 mcg were distributed in the reporting period (approximately (b)(4) women-years of exposure).

Suspected Unexpected Serious Adverse Reactions (SUSARs) reported for Vagifem® 25 mcg include the following:

- Angina pectoris in a 67 year old female in the United Kingdom treated for an unknown period of time

- Peripheral edema in a 54 year old female in the United Kingdom treated for 4 days
- Uterine cancer in a female of unknown age in the U.S. treated for an unknown period of time
- Metastases to bone in a 64 year old female in the U.S. treated for 18 months plus, history of breast cancer (2 separate diagnoses)
- Retinal vein occlusion in a female of unknown age in the U.S. treated for an unknown period of time
- Angioedema in a 67 year old female in the U.S. treated since year 2006
- Breast enlargement in a female of unknown age in the U.S. treated weekly since year 2008

One case of pulmonary embolism (PE) in a 70 year old woman in the U.S. treated for an unknown period with a history of a PE 13 years previously was reported for Vagifem® 25 mcg during the PSUR reporting period.

Vagifem® 10 mcg received market authorization in Canada on April 23, 2009.

Medical Officer's Comments:

Per the May 28, 2009 submission, there have been no rejections or restrictions to distribution for safety reasons during the reporting period (April 1, 2008 to March 31, 2009) for Vagifem® 25 mcg. No actions have been taken for safety reasons during the reporting period.

The treatment-emergent adverse events and the serious adverse events reported in the PSUR are not assessed as a cause for safety concern.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-related adverse events have been discussed previously in Section 7.1.3 "Dropouts and Other Significant Adverse Events", Subsection 7.1.3.3 "Other significant adverse events". Refer to these subsections for information on selected drug-related adverse events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The reported endometrial safety data for 52-week Study VAG-2195 and 52-week Study VAG-1748 for the 10 mcg estradiol vaginal tablet was pooled and evaluated in the ISS submitted on July 2, 2009.

7.4.1.1 Pooled data vs. individual study data

The reported endometrial safety data for 52-week Study VAG-2195 and 52-week Study VAG-1748 for the 10 mcg estradiol vaginal tablet was pooled and evaluated in the ISS submitted on July 2, 2009.

7.4.1.2 Combining data

The reported endometrial safety data for 52-week Study VAG-2195 and 52-week Study VAG-1748 for the 10 mcg estradiol vaginal tablet was pooled and evaluated in the ISS submitted on July 2, 2009.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The issue of dose dependency of reported adverse events has been discussed in several sections of this review, particularly in Section 7.1.2 "Other Serious Adverse Event", and Section 7.1.3 "Dropouts and Other Significant Adverse Events".

7.4.2.2 Explorations for time dependency for adverse findings

Exploration of time-dependent adverse event in 12-month Study VAG-2195 and 12-month Study VAG-1748 do not demonstrate any positive associations. The use of unopposed estrogen in a woman with a uterus increases the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. One case each of endometrial cancer and complex hyperplasia without atypia was reported in Study VAG-2195 (see Subsection 7.1.3.3 "Other significant adverse events", Endometrial Biopsy.

Although the Applicant reports no hyperplasia or cancer in 12-month Study VAG-1748, the DRUP safety review team disagrees (consisting of the medical team leader, the primary reviewer, and a second reviewer who is a board-certified gynecologic pathologist). One case of complex hyperplasia without atypia occurred in Study VAG-1748 (see Subsection 7.1.3.3 "Other significant adverse events", Endometrial Biopsy, for information for Subject (b)(6) diagnosed with complex hyperplasia without atypia.

Medical Officer's Comments:

In Study VAG-2195, Subject (b)(6) treated with 10 mcg estradiol vaginal table,) was diagnosed with complex hyperplasia without atypia on study day 43. Subject (b)(6) reportedly took study medication for 9 days. Per the information provided, the screening endometrial biopsy specimen

for Subject (b)(6) was reported as polyps (specimen obtained on day -37 (b)(6)). Three separate, blinded pathologists examined the baseline endometrial sample. Pathologist 1 reported an inactive endometrium. Pathologist 2 reported an inactive endometrium and atrophic type polyp. Pathologist 3 reported inactive to weak proliferation. Because there was no agreement between the three pathologists, the most severe pathologic diagnosis (atrophic polyp) became the final baseline diagnosis. Subject (b)(6) end-of-study endometrial biopsy (specimen obtained on (b)(6)) was reported as complex hyperplasia without atypia (Pathologist 1 reported inactive to weak proliferation, Pathologist 2 reported complex hyperplasia without atypia, may be hyperplastic polyp, and Pathologist 3 reported limited endometrium with focal area of glandular crowding without cytologic atypia). The reported baseline endometrial biopsy findings and the causality of complex hyperplasia without atypia in Subject (b)(6) is questionable.

7.4.2.3 Explorations for drug-demographic interactions

No drug-demographic interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

7.4.2.4 Explorations for drug-disease interactions

Per the submission, no drug-disease interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

7.4.3 Causality Determination

See Subsection 7.1.3.3 “Other Significant Adverse Events” for information regarding endometrial thickness (page 36) and endometrial biopsy (page 39) and 10 mcg estradiol vaginal tablets use.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

(b)(4)

the Applicant requested approval of the 10 mcg estradiol vaginal tablet administered daily for 2 weeks followed by twice-weekly administration.

8.2 Drug-Drug Interactions

No drug-drug interactions studies were performed as part of the 10 mcg estradiol vaginal tablet development program.

8.3 Special Populations

No pharmacokinetic studies were conducted in special populations, including subjects with renal or hepatic impairment.

Based on data from comparable estrogen therapy products, no formal studies in humans on the effect of 10 mcg estradiol vaginal tablet on reproduction or pregnancy were performed. Similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified.

8.4 Pediatrics

Estradiol vaginal tablet 10 mcg is not indicated for use in a pediatric population.

8.5 Advisory Committee Meeting

There was no advisory committee meeting in which 10 mcg estradiol vaginal tablet was discussed.

8.6 Literature Review

Literature relevant to estrogen therapy has been referenced in this review as needed. There is no need for a separate comprehensive review of the literature.

8.7 Postmarketing Risk Management Plan

There is no need for a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no relevant materials that are not included in other sections of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

This reviewer recommends the approval of the 10 mcg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions for the treatment of atrophic vaginitis due to menopause based on the data presented in the re-submission of Supplemental NDA 20-908/SE1-013. The re-submission re-analysis of the Applicant's intent-to-treat (ITT) study population (defined by the Applicant as all randomized subjects who take at least one dose of trial medication and have baseline and at least one post-baseline efficacy assessment) using last observation carried forward (LOCF) for the composite of all most bothersome symptoms provides sufficient evidence to conclude that the 10 mcg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions demonstrates a statistically significant mean change, compared to the placebo vaginal tablet, in this composite symptom endpoint ($p=0.002$). A statistically significant mean change in vaginal superficial and parabasal cells and vaginal pH score between baseline and week 12 (LOCF) for the 10 mcg estradiol vaginal tablet, compared to the placebo vaginal tablet, was also demonstrated ($p<0.001$ for both of these endpoints). Vagifem® (estradiol vaginal tablet) 25 mcg was approved on March 26, 1999 for the treatment of atrophic vaginitis based on similar considerations and is currently marketed in the U.S.

The safety of the 10 mcg estradiol vaginal tablet was not a concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved to (b)(4).

9.2 Recommendation on Regulatory Action

sNDA 20-908/SE1-013 is recommended for approval for the treatment of atrophic vaginitis due to menopause.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No Phase 4 clinical study commitment is proposed.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

See the *Medical Officer's Comments* on page 31 of this review for information regarding Table 6 in labeling for the Vagifem® 25 mcg dosage strength. This reviewer recommends approval of the labeling submitted by the Applicant on November 18, 2009 and amended on November 20, 2009 with the Applicant's written concurrence.

9.5 Comments to Applicant

None.

APPENDICES

9.6 Review of Individual Study Reports

The complete review of primary Phase 3a Study VAG-2195 and Phase 1 Study VAG-1850 can be viewed in the Medical Officer's Primary Review, dated October 6, 2008. The review of Study VAG-1748 is included in this review.

9.7 Line-by-Line Labeling Review

See the final agreed upon labeling.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THERESA H VAN DER VLUGT
11/20/2009

SHELLEY R SLAUGHTER
11/20/2009

I concur with Dr. van der Vlugt's recommendation that this 10 mcg estradiol tablet for vaginal use be approved for the treatment of atrophic vaginitis. Please, also see the Cross Discipline Team Leader's review for the rationale behind my concurrence.

CLINICAL REVIEW

Application Type	Supplemental NDA
Submission Number	20-908
Submission Code	SE2-013
Letter Date	December 7, 2007
Stamp Date	December 7, 2007
PDUFA Goal Date	October 7, 2008
Reviewer Name	Theresa H. van der Vlugt, MD
Review Completion Date	August 7, 2008
Review Finalized	October 6, 2008
Established Name	Estradiol vaginal tablet
Trade Name	Vagifem®
Therapeutic Class	Estrogen
Applicant	Novo Nordisk, Inc.
Priority Designation	3S
Formulation	Vaginal tablet
Dosing Regimen	One 10 microgram (mcg) estradiol vaginal tablet inserted intravaginally daily for two weeks, then one tablet inserted twice weekly
Indication	 (b)(4)
Intended Population	Postmenopausal women

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewer does not recommend approval of the 10 mcg estradiol vaginal tablet for the (b)(4) Sufficient evidence was not provided in the application to conclude that the 10 mcg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions was efficacious in (b)(4) (b)(4) The safety of the 10 mcg estradiol vaginal tablet was not a major concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved (b)(4) .

(b)(4) (b)(4) the Agency's 2003 draft Guidance for Industry entitled "Estrogen and ogestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that:

1. have appropriate inclusion and exclusion criteria;
2. conduct appropriate study analyses; and
3. evaluate the following three co-primary endpoints:

- Mean change from baseline to week 12 in the vaginal Maturation Index (proportions of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a vaginal smear. The primary efficacy analysis should show a statistically significant increase in superficial cells and a corresponding statistically significant decrease in parabasal cells.

- Mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants would have a vaginal pH > 5.0. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.

- Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy include:

  1. Vaginal dryness (categorized as none, mild, moderate or severe).

2. Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate or severe).
3. Vaginal pain associated with sexual activity (categorized as none, mild, moderate or severe).
4. Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate or severe).

The Division of Reproductive and Urologic Products (DRUP) accepts that for number 3 above (vaginal pain associated with sexual activity) and number 4 above (vaginal bleeding associated with sexual activity) that a subject's response might be NA = not applicable because of the absence of sexual activity in the reporting period.

Novo Nordisk Inc., 100 College Road West, Princeton, NJ 08540 is the Applicant for sNDA 20-908/SE2-013.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 clinical study is proposed.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Vagifem® (estradiol vaginal tablet) 25 mcg was approved in the U.S. on March 26, 1999 for the treatment of atrophic vaginitis and became commercially available in year 2000. Data from two 12-week clinical trials (VAG/PD/9/USA [placebo-controlled] and VAG/PD/5/CAN [active-controlled]), conducted during the development program, supported the approval of 25 mcg Vagifem®. The 10 mcg estradiol vaginal tablet was included in these clinical trials as a minimum control dose. In these two clinical trials, treatment with the 10 mcg estradiol vaginal

tablet was reported to "increase the cellular maturation of the vaginal epithelium and provided evidence of atrophic vaginitis symptom relief."

The investigational new drug (IND) application (IND [(b)(4)] for the clinical evaluation of the 10 mcg estradiol vaginal tablet was submitted to DRUP on [(b)(4)]. Two studies have been conducted under IND [(b)(4)] Phase 3a Study VAG-2195, "A 12 month double-blind, randomized, parallel-group, placebo-controlled, multicenter trial to investigate the efficacy and safety of Vagifem Low Dose (10µg 17beta-estradiol vaginal tablet) for the treatment of postmenopausal atrophic vaginitis symptoms" and Phase 1 Study VAG-1850, "A Pharmacokinetic Randomized Study with a Parallel Group Design to Assess the Extent of Systemic Absorption of Estradiol During Treatment with a 10 µg or 25 µg Estradiol Vaginal Tablet Administered Once Daily for 2 Weeks Followed by 10 Weeks of Twice-Weekly Maintenance Therapy in Postmenopausal Women with Atrophic Vaginitis".

The primary source of efficacy data submitted in this efficacy supplement in support of a [(b)(4)] is single, 52-week Phase 3a Study VAG-2195. In Study VAG-2195, subjects were randomized to receive:

- Estradiol vaginal tablet, 10 mcg (one vaginal tablet inserted daily for 2 weeks and then one vaginal tablet inserted twice-weekly thereafter)
- Placebo vaginal tablet (one vaginal tablet inserted daily for 2 weeks and then one vaginal tablet inserted twice-weekly thereafter)

Two sources of safety data were submitted in sNDA 20-908/SE2-013: Phase 3a Study VAG-2195 and Phase 1 Study VAG-1850. A total of 308 treated subjects are represented in 52-week Study VAG-2195: 205 subjects were treated with 10 mcg estradiol vaginal tablets and 103 subjects were treated with Placebo vaginal tablets. A total of 57 subjects were treated in Study VAG-1850: 29 subjects received 10 mcg estradiol vaginal tablets and 28 subjects received Vagifem® 25 mcg.

1.3.2 Efficacy

The Agency requested data submitted by the Applicant on January 25, 2008, corrected by the Applicant on April 17, 2008, that included analyses of mean change from baseline to week 12 for those subjects who, at baseline,:

- had no more than 5 percent superficial cells on a lateral wall vaginal smear
- had a baseline vaginal pH of 5 or greater
- reported a moderate to severe most bothersome vaginal symptom with a severity score of 2 or greater (based on a severity score of moderate = 2 and severe = 3)

The vaginal Maturation Index results from this subset analysis from the first 12 weeks of 52-week Study VAG-2195 demonstrate the effectiveness of the 10 mcg estradiol vaginal tablet

versus the Placebo vaginal tablet in producing a statistically significant increase in vaginal superficial cells ($p<0.001$), and a corresponding statistically significant decrease in vaginal parabasal cells ($p<0.001$). The mean change from baseline to week 12 in the vaginal Maturation Index (proportion of superficial and parabasal cells) is one of the recommended co-primary endpoints for a VVA indication.

The vaginal pH results from this subset analysis, represented as a vaginal pH score (scaled as: pH < 5 = no atrophy x 0, pH of 5-5.49 = mild atrophy x 1, pH of 5.5-6.49 = moderate atrophy x 2, and pH of ≥ 6.49 = severe x 3), from the first 12 weeks of 52-week Study VAG-2195 demonstrate the effectiveness of the 10 mcg estradiol vaginal tablet versus the Placebo vaginal tablet in producing a statistically significant reduction in the vaginal pH score between baseline and week 12 ($p<0.001$). The mean change from baseline to week 12 in vaginal pH is a recommended co-primary endpoint for a VVA indication. The use of a vaginal pH score was specified in the study protocol.

The most bothersome moderate to severe symptom results from this subset analysis from the first 12-weeks of 52-week Study VAG-2195 do not demonstrate the effectiveness of the 10 mcg estradiol vaginal tablet in producing a statistically significant reduction, compared to the Placebo vaginal tablet, for any of the vaginal symptoms assessed. Vaginal dryness, vaginal irritation/itching, vaginal soreness, dysuria, vaginal pain associated with sexual activity (dyspareunia), and vaginal bleeding associated with sexual activity were the symptoms assessed in Phase 3a Study VAG-2195.

During the review cycle, it was determined that the normality assumption for using an ANCOVA analysis, as specified in the Statistical Analysis Plan, was not met with the symptom data reported for vaginal dryness, vaginal irritation/itching, and pain associated with sexual activity (dyspareunia). Because of this, the Statistical Reviewer prepared an ANCOVA on ranks for these three symptoms. The analysis of the individual symptom of vaginal dryness, vaginal irritation/itching, and pain associated with sexual activity (dyspareunia) showed the following p-values, respectively: $p=0.0929$, $p=0.7140$ and $p=0.0200$. A statistical adjustment for multiple comparisons is necessary, however. After adjusting for multiplicity, treatment with the 10 mcg estradiol vaginal tablet does not demonstrated statistical improvement over the placebo vaginal tablet for the treatment of vaginal dryness, vaginal irritation/itching, and dyspareunia.

The three symptoms of vaginal soreness, dysuria, and vaginal bleeding associated with sexual activity were not analyzed for effectiveness due to the limited number of subjects who identified these symptoms as moderate to severe and most bothersome at baseline. The mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the subject as being the most bothersome to her is a co-primary endpoint for a VVA indication.

The reviewer does not recommend approval of the 10 mcg estradiol vaginal tablet for the (b)(4) The Agency's recommended co-primary endpoints of mean change in vaginal superficial and parabasal cells as well as the mean change in vaginal pH were met in the primary Phase 3a Study VAG-2195. However, the recommended co-primary endpoint, reduction in the

severity of the moderate to severe and most bothersome vaginal symptom, was not met in the submission.

1.3.3 Safety

The safety data presented in the submission demonstrates an acceptable overall safety profile of the 10 mcg estradiol vaginal tablet, administered intravaginally daily for two weeks and then twice-weekly thereafter.

No deaths occurred during the conduct of 52-week Study VAG-2195 or 12-week Study VAG-1850.

In total, 7 subjects experienced serious adverse events (SAEs) in Study VAG-2195 (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [2.4%, 5 of 205 treated subjects] and 2 subjects in the placebo vaginal tablet treatment group [2%, 2 of 103 treated subjects]). No subject in Study VAG-1850 experienced an SAE. The SAEs reported in Study VAG-2195 do not raise safety concerns.

1.3.4 Dosing Regimen and Administration

Vagifem® 25 mcg (estradiol vaginal tablet), administered intravaginally daily for 2 weeks then twice-weekly thereafter, is approved for the treatment of atrophic vaginitis, and is only intended for intravaginal use in postmenopausal women.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

In vitro and in vivo studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling

1.3.6 Special Populations

Estradiol vaginal tablet (10 mcg) is only intended for use in postmenopausal women. In Phase 3b Study VAG-2195, conducted for the 10 mcg estradiol vaginal tablet dosing regimen, there was an insufficient numbers of geriatric subjects to determine if those over 65 years of age differ from younger subjects in their response to 10 mcg estradiol vaginal tablets..

Estradiol vaginal tablet (10 mcg) was not studied in women with liver disease or renal impairment. Estradiol vaginal tablet (10 mcg) should not be used in pregnant women.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vagifem® (estradiol vaginal tablet) 25 mcg was approved in the U.S. on March 26, 1999 for the treatment of atrophic vaginitis and became commercially available in year 2000. Per the Medical Officer's Review, data from two 12-week clinical trials (VAG/PD/9/USA [placebo-controlled] and VAG/PD/5/CAN [active-controlled]), conducted during the development program, supported the approval of 25 mcg Vagifem® The 10 mcg estradiol vaginal tablet was included in these clinical trials as a minimum control dose. In these two clinical trials, treatment with the 10 mcg estradiol vaginal tablet was reported to "increase the cellular maturation of the vaginal epithelium and provided evidence of atrophic vaginitis symptom relief." These reported findings stimulated product development for the 10 mcg estradiol vaginal tablet for (b)(4) (b)(4)

The results of two completed clinical trials are included in this submission: 1) Phase 3a Study VAG-2195 assessed safety and effectiveness of the 10 mcg estradiol vaginal tablet in postmenopausal women with signs and symptoms of atrophic vaginitis; 2) Phase 1 Study VAG-1850 was an open label, single center, multiple dose clinical trial conducted to evaluate the systemic estradiol absorption of the 10 mcg estradiol vaginal tablet. Study VAG-1850 provides supporting evidence of safety.

2.2 Currently Available Treatment for Indications

Numerous estrogen alone and estrogen plus progestin drug products are currently approved for the treatment of vulvar and vaginal atrophy (VVA) due to menopause and/or the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause. These include:

- Oral tablet: Activella® (estradiol plus norethindrone acetate), Angeliq® (drospirenone plus estradiol), Cenestin® (synthetic conjugated estrogens, A), Enjuvia™ (synthetic conjugated estrogens, B), Estrace® (estradiol), femhrt® (norethindrone acetate/ethinyl estradiol), Femtrace® (estradiol acetate), Menest® (esterified estrogens), Ortho-Est® (estropipate), Prefest® (estradiol/norgestimate), Premarin® (conjugated estrogens), Prempro™/Premphase® (conjugated estrogens plus medroxyprogesterone acetate)

- Transdermal system: Alora® (estradiol), Climara® (estradiol), Climara-Pro® (estradiol plus levonorgestrel), Combipatch™ (estradiol plus norethindrone acetate), Esclim® (estradiol), Estraderm® (estradiol), Vivelle® (estradiol), Vivelle-Dot® (estradiol)

- Topical: Divigel® (estradiol gel), Elestrin™ (estradiol gel), Estrasorb® (estradiol topical emulsion), EstroGel® (estradiol gel), Evamist™ (estradiol mist)

- Vaginal: Premarin® Vaginal Cream (conjugated estrogens cream), Estrace® Cream (estradiol cream), Vagifem® (estradiol hemihydrate tablet), Estring® IVR (estradiol ring), Femring® (estradiol ring).

2.3 Availability of Proposed Active Ingredient in the United States

The following oral estradiol products are approved and currently marketed in the U.S for the treatment of vulvar and vaginal atrophy (VVA):

Estradiol alone oral product:	Dosage strengths:
Estrace® (estradiol)	0.5 mg, 1.0 mg, 2.0 mg
Estradiol plus progestin oral product:	
Activella® (estradiol/norethindrone acetate)	1.0 mg/0.5 mg, 0.5 mg/0.1 mg
Angeliq® (estradiol/drospirenone)	1.0 mg/0.3 mg
Prefest® (estradiol/estradiol plus norgestimate)	1.0 mg/ 1.0 mg plus 0.09 mg
Estradiol alone transdermal system:	
Alora® (estradiol)	0.025 mg, 0.05 mg, 0.075 mg, 0.1 mg
Climara® (estradiol)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
Esclim® (estradiol)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
Estraderm® (estradiol)	0.05 mg, 0.1 mg
Vivelle® (estradiol)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
Vivelle-Dot® (estradiol)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, 0.1 mg
Estradiol plus progestin transdermal system	
Combipatch® (estradiol/norgestimate)	0.05 mg/0.14 mg, 0.05 mg/0.25 mg
Climara Pro® (estradiol/levonorgestrel)	0.045 mg/0.015 mg
Topical products:	
EstroGel® (estradiol gel)	0.075 mg
Vaginal products:	
Estrace® Vaginal Cream (estradiol)	0.1 mg
Estring® (estradiol vaginal ring)	7.5 mcg
Vagifem® (estradiol hemihydrate)	25 mcg

2.4 Important Issues With Pharmacologically Related Products

After an average follow-up of 5.2 years, the conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) substudy of the Women's Health Initiative (WHI) study was stopped early (year 2002) because the increased risk of breast cancer and cardiovascular events exceeded the pre-specified limits in the "Global Index". Centrally adjudicated data, after an average follow-up of 5.6 years, reported an increased risk of invasive breast cancer (relative risk [RR] of 1.24 with a 95% nominal confidence interval [nCI], 1.01-1.54), increased risk of all stroke (RR 1.31, 95% CI, 1.02-1.68) and ischemic stroke (RR 1.44, 95% CI, 1.09-1.90), increased risk of coronary heart disease (RR 1.23, 95% CI, 0.99-1.53), increased risk of probable dementia (RR 2.05, 95 percent CI, 1.21-3.48), and a decreased risk of hip fracture (RR 0.67, 95 percent CI, 0.47-0.96).

The risk and benefit information available in the WHI substudy in year 2002 prompted changes in labeling for estrogen class drug products including, but not limited to, the addition of a boxed warning to all estrogen plus progestin product labels and the expansion of the existing boxed warning in all estrogen alone product labels to include the increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis reported in the estrogen plus progestin WHI substudy. In addition, boxed warning information states that "---in the absence of comparable data, these risks should be assumed to be similar" for "other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestin", and that "---estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women."

After an average follow-up of 6.8 years, the conjugated estrogens alone WHI substudy was also stopped early (year 2004) because the use of CE alone increased the risk of stroke (RR 1.39, 95% nCI, 1.10-1.77) (conjugated estrogens alone versus placebo), and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Other findings in the conjugated estrogens alone clinical trial included a decreased risk of hip fracture (RR 0.61, 95% nCI, 0.41-0.91), no effect on coronary heart disease (RR 0.91, 95% nCI 0.75-1.12), a decreased risk of invasive breast cancer (RR 0.77, 95% nCI, 0.59-1.01), an increased risk of probable dementia (RR 1.49, 95% nCI, 0.83-2.66), and no decrease in mild cognitive impairment (RR 1.34, 95% CI, 0.95-1.89).

Centrally adjudicated results reported for the WHI estrogen alone substudy, after an average follow-up of 7.1 years, reported an increased risk for all stroke (RR 1.37, 95% nCI, 1.09-1.73) (CE versus placebo) and ischemic stroke (RR 1.55, 95% nCI, 1.19-2.01). No effect on coronary heart disease, after an average follow-up of 7.1 years, was reported (RR 0.95, 95% nCI, 0.78-1.16). Other findings in the CE alone substudy, based on an average follow-up of 7.1 years, included a decreased risk of hip fracture (RR 0.65, 95% nCI, 0.45-0.94), a decreased risk of invasive breast cancer (RR 0.80, 95% nCI, 0.62-1.04), and an increased risk for probable dementia (RR 1.49, 95% CI, 0.83-2.66).

The risk and benefit information available in the estrogen alone WHI substudy in year 2004 prompted changes in labeling for estrogen class drug products including, but not limited to, the expansion of the boxed warning to include the reported increased risk of stroke in the estrogen alone WHI substudy. In years 2006 and 2007, additional changes were made in labeling for estrogen class drug products based on centrally adjudicated results for the estrogen alone WHI substudy.

Risk information available in the Women's Health Initiative Memory Study (WHIMS) in years 2003 and 2004 prompted additional changes in labeling for estrogen class drug products to include the reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older. WHIMS findings for both the estrogen alone ancillary study and the estrogen plus progestin ancillary study were added to the boxed warning, and the clinical studies, warnings and precautions sections of estrogen class labeling.

2.5 Presubmission Regulatory Activity

Phase 3a Study VAG-2195 entitled, "A 12 month, double-blind, randomized, parallel-group, placebo-controlled, multi-center trial to investigate the efficacy and safety of Vagifem Low Dose (10μg 17β-estradiol vaginal tablet) for the treatment of postmenopausal atrophic vaginitis symptoms" was a prospective study conducted at 51 U.S. sites and 4 Canadian sites. Three hundred and nine (309) subjects were randomized (2:1; active drug: placebo) to received either 10 mcg estradiol vaginal tablet (205 subjects) or placebo vaginal tablet (104 subjects) for 12 months. The treatment regimen included the vaginal insertion of a single tablet daily for 2 weeks (14 days) followed by a twice weekly administration for the remainder of the study period (50 weeks). The same treatment regimen is utilized for approved Vagifem® 25 mcg. Study participants were allowed to use sponsor-provided vaginal lubricant, as needed, after the completion of the first 12 weeks of Study VAG-2195.

The primary objective of Study VAG- 2195, originally submitted on (b)(4) under IND (b)(4) was to evaluate the efficacy of 10 mcg estradiol vaginal tablet compared to placebo "as assessed by the clinical symptoms and the objective parameters." The secondary objective of Study VAG-2195 was to "evaluate the endometrial safety from endometrial biopsies taken at the beginning and at the end of study treatment (12 months)."

In a letter dated February 1, 2005, the Division of Reproductive and Urologic Products (DRUP) provided Novo Nordisk with numerous comments and recommendations regarding Study VAG-2195. In particular, Novo Nordisk was advised that:

1) "Per the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", for a moderate to severe symptoms of vulvar and vaginal atrophy indication, the Agency recommends three equal co-primary endpoints as follows:

1. Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being most bothersome to her.
2. Mean change from baseline to week 12 in vaginal pH.
3. Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells).

2) For estrogen alone drug products intended to treat moderate to severe symptoms of vulvar and vaginal atrophy, the Agency's 2003 draft clinical evaluation guidance document recommends that effectiveness be demonstrated in all three co-primary endpoints as follows:

   a. End-of-study results should demonstrate a statistically significant improvement versus placebo in the one moderate to severe vaginal symptom self-identified by the subject as most bothersome to her at baseline. We recommend that the subject complete an independent self-administered questionnaire to include the following categories;

      - Vaginal dryness (recorded as none, mild, moderate, or severe)
      - Vaginal and/or vulvar irritation/itching (recorded as none, mild, moderate, or severe)
      - Dysuria (recorded as none, mild, moderate, or severe)
      - Vaginal pain associated with sexual activity (if sexually active and recorded as none, mild, moderate, or severe)
      - Vaginal bleeding associated with sexual activity (if sexually active and recorded as none, mild, moderate, or severe)

      The subject should be instructed to identify the one vaginal symptom, ranked as moderate to severe at baseline, which is most bothersome to her. At end-of-study (week 12 or final visit), we recommend that the subject complete a similar questionnaire. We do not recommend that an average score of the three vaginal symptoms; namely, dryness, soreness, and irritation be calculated

   b. End-of-study results should demonstrate a statistically significant improvement versus placebo in vaginal pH.

   c. End-of-study results should demonstrate a statistically significant decrease of parabasal cells and a corresponding statistically significant increase in superficial epithelial cells.

3) Be advised that the stated secondary and other endpoints would not be considered in [redacted] (b)(4) (b)(4)

4) Per the Agency's 2003 draft clinical evaluation guidance document, we recommend that subjects should be enrolled who have self-identified at least one moderate to severe vaginal symptom. You may, however, retain the inclusion criteria – "at least three moderate to severe symptoms of vulvar/vaginal atrophy" if you prefer.

5) The Agency recommends that when a TVUS is obtained at baseline as an inclusion criterion that a double-wall endometrial thickness of < 4 mm be considered (not < 5 mm as proposed).

6) You are advised to conduct a vaginal pH assessment at week 12 as a co-primary endpoint per the Agency's 2003 draft clinical evaluation guidance document.

7) The Agency recommends that a self-administered questionnaire be developed to include the following symptom categories; vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. Subjects should be instructed to self-identify the symptom most bothersome to her. We recommend that subjects not be asked by the clinic staff to indicate her experience with symptoms they may have experienced and the severity of such symptoms. A verbal challenge by clinic staff may unduly influence the subject's response and bias the information. We do recommend, however, that severity definitions be reviewed with the subject prior to completion of the self assessed questionnaire, such as proposed in Study VAG-2195.

8) We do not recommend that a composite symptom score, as proposed, be calculated.

9) As per the Agency's 2003 clinical evaluation guidance document, to demonstrate effectiveness of the drug product versus placebo, we recommend that study results show a statistically significant increase in superficial epithelial cells as obtained by conducting lateral wall vaginal cytology smears at baseline and week 12.

10) Confirm that a vaginal pH assessment will be completed at week 12 as one of the three co-primary endpoints (not as a proposed secondary endpoint).

11) We recommend that an end-of-study mammogram be performed for all subjects with a time lapse of 12 months from her last mammogram.

12) The safety assessments as proposed appear appropriate."

On February 21, 2005, Novo Nordisk submitted Amendment 1 for Study VAG-2195. Per the submission, "several substantial changes have been made" to address the Agency's February 1, 2005 comments. The changes included:

- "The primary and other efficacy assessments have been redefined according to agency guidelines.
- The urogenital symptoms have been modified and will be captured as a questionnaire to be completed by the subject.
- The entry criteria for endometrial thickness has changed according to agency guidelines.
- A bilateral mammogram has been added to the end of study visit to help assess the subject's safety by evaluating any possible change to the subject's mammogram for the duration of the study."

- The laboratory assessments to assess haemostasis parameters for factor V Leiden, protein-C and protein-S have been removed from the study and will no longer be assessed.
- The use of vaginal lubricants following the week 12 assessment has been included to allow symptomatic relief to subjects.
- The protocol was updated and all of the changes delineated in this amendment are included in Version 4 of the protocol."

Amendment 2 for Study VAG-2195 was submitted on February 3, 2006. Per Amendment 2, due to slow enrollment, the following protocol changes were made:

- The trial population was reduced from a total of 600 (400 treated with estradiol vaginal tablet and 200 treated with placebo vaginal tablet) to a total of 300 (200 treated with estradiol. vaginal tablet and 100 treated with placebo vaginal tablet).
- Planned completion of the clinical trial report changed from January 2007 to July 2007.

Medical Officer's Comments:

Due to an oversight, no clinical or statistical comments were provided regarding the reduction in the clinical trial population.

Additional changes made in Amendment 2 for Study VAG-2195 included, but are not limited to, the following:

- Subjects will be asked to bring empty blister packages (not just empty applicators) and unused medication packages to visit 2 through 9 for drug accountability.
- Prohibited medications to include vaginal preparations of any kind (except vaginal lubricant provided by Novo Nordisk after week 12).
- The endometrial biopsies data will be pooled together with the endometrial biopsies data from the planned VAG-1748 study to provide the overall endometrial safety assessment for 10 mcg estradiol vaginal tablet.

On September 18, 2007, DRUP conveyed to Novo Nordisk its recommendation that they request a preNDA meeting for the 10 mcg estradiol vaginal tablet product. No request for a preNDA meeting was forthcoming from Novo Nordisk, however.

In a letter dated November 15, 2007, DRUP provided Novo Nordisk with the following information regarding the primary efficacy analysis for the indication of the (b)(4) (b)(4):

a. "The most bothersome symptom co-primary endpoint should be based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms.
b. The patient population to be analyzed for the primary efficacy analysis should meet enrollment criteria for (1) vaginal pH (pH greater than 5), (2) vaginal cellular maturation

(no greater than 5% superficial cells), and (3) identification of a moderate to severe most bothersome symptom.

c. We remind you of the information that was provided to you in our communication of February 1, 2005. This information included the following guidance in Item 8: "We do not recommend that a composite symptom score, as proposed, be calculated."
d. In accordance with our recommendation that a composite score not be used for the co-primary endpoint, your clinical trial should demonstrate that, compared to subjects treated with placebo, subjects treated with Vagifem 10 µg vaginal tablets have a statistically significant improvement in one or more of the individual symptoms listed in Item 1 a above, as well as a statistically significant decrease in vaginal pH, and increase in vaginal superficial cells, and a decrease in vaginal parabasal cells."

In addition, the November 15, 2007 letter requested that a final Statistical Analysis Plan (SAP) for Study VAG-2195 be submitted for review and comments prior to the submission of the supplemental NDA. The SAP was not submitted prior to the sNDA 20-908/SE2-013 submission.

NDA 20-908/SE2-013 was submitted on December 7, 2007. In the submission's cover letter, Novo Nordisk asserted that the following items had been addressed:

"1a) the most bothersome symptom co-primary endpoint is based on one or more of the following individual symptoms: vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, vaginal dryness, and vaginal irritation/itching and not on a composite of symptoms.

1b) the patient population to be analyzed for the primary analysis meets the enrollment criteria for (1) vaginal pH (pH greater than 5), (2) vaginal cellular maturation (no greater then 5% superficial cells), and (3) identification of a moderate to severe most bothersome symptom.

1c) as recommended a composite symptom score was <u>not</u> calculated or used as a co-primary endpoint.

1d) as per the Division's recommendation the data were analyzed to demonstrate that subjects treated with Vagifem 10 µg vaginal tablets as compared to placebo showed statistically significant improvement from baseline to week 12 in:

- the moderate to severe symptom that has been identified by the patient as being the most bothersome to her
- lowering of vaginal pH
- vaginal Maturation Index

2) as requested, a Statistical Analysis Plan (SAP) for VAG-2195 is included in this submission."

Novo Nordisk also requested in the December 7, 2007 cover letter for sNDA 20-908/SE2-013 that the Division address [redacted]

Medical Officer's Comments:

In an amendment to [redacted], Novo Nordisk agreed with the Agency's recommended estrogen class labeling revisions (provided on September 4, 2007) with the following exceptions:

1. *The following text was deleted from the Dosage and Administration section of the physician insert: "[redacted]*
2. *The following text was moved from the [redacted] section of the label: [redacted]*
3. *The following text in the Dosage and Administration section of the physician insert was modified as shown: "Use of estrogen, ~~alone or in combination with a progestin,~~ should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. [redacted]*
4. *The following text was deleted in the patient insert under "What can I do to lower my chances of a serious side effect with Vagifem?": "If you have a uterus, talk with your healthcare provider about whether the addition of a progestin [redacted] is right for you. The addition of a progestin is generally recommended for women with a uterus to reduce the chance of getting cancer of the Uterus".*

Labeling Supplement [redacted] for Vagifem® 25 mcg received approvable action letters from the Agency on [redacted] As a part of the review of sNDA 20-908/SE2-013, Novo Nordisk requested that [redacted] labeling be addressed in the combined label for the Vagifem® 25 mcg and the 10 mcg estradiol vaginal tablet products included in the submission.

2.6 Other Relevant Background Information

Vagifem® 25 mcg has been marketed in the United States since year 2000.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Per the approved labeling, 25 mcg Vagifem® (estradiol vaginal tablets) are small, white, film-coated tablets containing 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol. Each tablet contains the following inactive ingredients: hypromellose, lactose monohydrate, maize starch and magnesium stearate. The film coating contains hypromellose and polyethylene glycol. Each white tablet is 6 mm in diameter and is placed in a disposable applicator. Each tablet-filled applicator is packaged separately in a blister pack.

The estradiol drug substance and inactive ingredients in the 10 mcg estradiol vaginal tablets used in Phase 3a Study VAG-2195 are the same as in the approved Vagifem® 25 mcg tablet except for the reduction in the amount of estradiol (b)(4) (b)(4) is the (b)(4) (b)(4) (b)(4) ."

Each 10 mcg estradiol vaginal tablet contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol. The packaging utilized in Study VAG-2195 was the same as the marketed product.

Per the submission, the production of 10 mcg estradiol vaginal tablets will be performed in production site C2 in Maaloev, Denmark. "The manufacturing equipment, batch size and production facilities at Maaloev are approved for some ex-US markets for production of Vagifem 0.025 mg tablets. The quality of the production of Estradiol 0.010 mg vaginal tablets in the production site Maaloev, Denmark was validated by a process validation on three production size batches."

The sNDA submission confirms that "The batches used for clinical studies are produced in production size by the same formulation and with the same manufacturing equipment as intended for the market."

Medical Officer's Comments:

Per the Chemistry, Manufacturing and Controls (CMC) Reviewer, an Environmental Assessment section has been provided and is acceptable as follows:

"The sponsor claims a categorical exclusion from the requirement for an environmental assessment. A justification is provided that the maximum is (b)(4) estradiol."

Per the CMC Reviewer, an information request to the Applicant is warranted. On August 6, 2008, the following information request was made:

"The drug product specification submitted in SE2-013 is stated to be approved, but is, instead, the specification provided to S-014. Currently, S-014 is Approvable, pending a demonstration of bioequivalence between the C2 and 5A batches for the 0,025 mg tablet.

(b)(4) (b)(4) The limits approved in the original NDA, therefore, should be used for the 10 mcg strength tablet. Provide an updated drug product specification for the 10 mcg tablet reflecting the approved limits for related substances.

The assay method, (b)(4) has been amended to change the volume of injection. Provide the following report: " (b)(4) Provide validation data to support the change in injection volume, and data to show that the change has resulted in improved precision and accuracy of the method."

The Applicant responded to the CMC request for information on August 28, 2008. See the Chemistry, Manufacturing and Controls (CMC) Review.

3.2 Animal Pharmacology/Toxicology

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Medical Officer's Comments:

Please refer to the original NDA 20-908 submission for animal pharmacology and toxicology information.

Per the Pharmacology/Toxicology Review and Evaluation dated May 21, 2008:

- *"No new toxicology studies were submitted and none are necessary."*
- *"Nonclinical safety issues relevant to clinical use: None."*
- *"Recommendation for nonclinical studies: None."*
- *"Recommendation on approvability: Pharmacology recommends approval of Vagifem (estradiol vaginal tablet) 10 µg."*
- *"Recommendation on labeling: Labeling will be similar to Vagifem (estradiol vaginal tablets) 25 µg approved under NDA 21-840, which has the same formulation composition and dosing schedule and is used for the same indication."*

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Study VAG-2195 was a double-blind, randomized 2:1 (active drug: placebo using an Interactive Voice Response System [IVRS]), multi-center, placebo-controlled, parallel-group clinical trial. The two treatment groups were 10 mcg estradiol vaginal tablet (205 subjects) and placebo vaginal tablet (104 subjects for a total of 309 subjects) for a treatment period of 52 weeks. One subject randomized to the placebo treatment group did not receive study drug. Therefore, the safety population for Study VAG-2195 was comprised of 308 subjects. Two hundred thirty-four (76%, 234 of 309 randomized subjects) completed the clinical trial. Seventy-five (75) subjects discontinued Study VAG-2195 (24%, 75 of 309 randomized subjects; 41 subjects in the 10 mcg estradiol vaginal tablet treatment group and 34 subjects in the placebo vaginal tablet treatment group). Most subjects completed 41 weeks or more of treatment in Study VAG-2195 (81.5%, 167 of 205 treated subjects in the 10 mcg estradiol vaginal tablet treatment group and 71%, 73 of 103 treated subjects in the placebo vaginal tablet treatment group).

Using the supplied applicator, each randomized subject inserted one 10 mcg estradiol vaginal tablet or placebo vaginal tablet once daily during the first two weeks of treatment followed by twice weekly administration for the remainder of the trial (50 weeks). Each 10 mcg estradiol vaginal tablet contained 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol and the following excipients: hypromellose, lactose monohydrate, maize starch and magnesium stearate. The film coating of the 10 mcg estradiol vaginal tablet contains hypromellose and polyethylene glycol. The placebo tablets contained the same excipients and film coating but no estradiol. Both active drug and placebo vaginal tablets were supplied by Novo Nordisk A/S, Denmark.

Each clinical site assessed the subject's compliance with study medication at visits 3 (week 2), 4 (week 4), 5 (week 8), 6 (week 12), 7 (week 26), 8 (week 39) and 9 (week 52). Compliance was determined through interviews and the number of blister packages returned. A subject was considered non-compliant if she missed more than 7 days of trial medication during one month or more than 20% of the trial medication over the entire treatment period.

4.2 Tables of Clinical Studies

Table 1 includes the 2 clinical trials conducted in the 10 mcg estradiol vaginal tablet development program.

Table 1: Vagifem Clinical Trials

Type of Study	Study Identifier	Objectives of Study	Study Design and Type of Control	Test Products, dosage Regimen, Route of	Number of Subjects: TOTAL	Healthy Subjects or Diagnosis of Patients	Duration of Treatment

				Administration			
Bioavailability	VAG-1850	To evaluate systemic estradiol absorption and safety	Single-center, randomized, open-label, multiple-dose, parallel-group trial Compare systemic absorption (plasma PK parameters) for 10 mcg estradiol vaginal tablet versus Vagifem 25 mcg tablet	**10 mcg tablet** Once daily for 2 weeks, followed by twice-weekly for 10 weeks **25 mcg tablet** Once daily for 2 weeks, followed by twice-weekly for 10 weeks	58 randomized 57 treated	Healthy postmenopausal women (60-70 years) with history of 5 years of amenorrhea or 2 years of surgical menopause, with E2 <20 pg/mL and FSH >40 mIU/mL, with signs and symptoms of atrophic vaginitis	12 weeks (2 weeks once-daily, 10 weeks twice-weekly)
Efficacy	VAG-2195	Efficacy and safety	Multi-center, randomized, double-blind, placebo-controlled, parallel-group trial Compared clinical efficacy and endometrial safety of 10 mcg estradiol vaginal tablet versus Placebo	**10 mcg tablet** Once daily for 2 weeks, followed by twice-weekly for 50 weeks **Placebo** Once daily for 2 weeks, followed by twice-weekly for 50 weeks	309 randomized 308 treated	Healthy postmenopausal women (45 years or older) ≥2 years after last menstruation; or bilateral oophorectomy performed ≥2 years before screening, with E2 <20 pg/mL and FSH <40 mIU/mL, ≤5 percent superficial cells, vaginal pH >5, endometrial thickness <4.0 mm and normal mammograms. Subjects had ≥3 urogenital symptoms and at least one of them had to be a moderate to severe symptom as identified by	52 weeks (2 weeks once-daily, 50 weeks twice-weekly)

						the patient.	

Source: NDA 20-908/SE2-013 dated 13 November 2007, Module 5.2, Tabular Listing of All Clinical Studies, page 3 of 3.
Definitions: mcg = microgram, E2 = estradiol, FSH = follicle stimulating hormone.

4.3 Review Strategy

The primary source of efficacy data submitted in support of a treatment (b)(4) (b)(4) is Phase 3a Study VAG-2195.

The primary source of safety data is Phase 3a Study VAG-2195 and 12-week Phase 1 Study VAG-1850. The safety data received on December 7, 2007 (sNDA 20-908/SE2-013) included safety results and conclusions related to treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, subject withdrawals, clinical laboratory parameters, vital sign measurements, transvaginal ultrasound (TVU) results, and endometrial biopsy results for the 12-month Study VAG-2195.

On April 3, 2008, Novo Nordisk submitted the 4-Month Safety Update with the following information:

- "VAG-1850 – no new or follow-up safety information as of 13 March 2008."
- "VAG-2195 – no new safety information; follow-up safety information only for four subjects/five cases as of 13 March 2008."

The 4-Month Safety Update also provided initial serious adverse events from an ongoing European safety trial, VAG-1748, being "conducted as per CHMP guidelines in support of the registration of Vagifem 10 µg tablets in Europe."

4.4 Data Quality and Integrity

Three audit certificates are included in the sNDA submission. On February 1, 2006, an internal audit was performed at Novo Nordisk, Inc. in New Jersey. Per the certificate, "The audit was conducted in accordance with CQA departmental procedures 3.02, Doc. No. 014651, edition 9.0. The audit of VAG-2195 included an audit conducted at Novo Nordisk, Inc., (NNI), Princeton, NJ. During the audit the content of the general trial master file was reviewed." The audit report dated March 13, 2006 indicated that "the clinical trial conducted at Novo Nordisk Inc. substantially meets the requirements of current FDA/ICH GCP standards". "Four minor nonconformities were noted."

On February 1-3, 2006, an internal audit was performed at study site 46 (New York, NY) for Dr. Nachtigall. Per the submission, "The audit was conducted in order to investigate compliance with current GCP, Novo Nordisk Policies and Clinical Trial SOPs, local guidelines/requirements

and local SOPs." The audit report dated April 30, 2006 indicated that "--- the audit team finds that the clinical trial conducted at Dr. Nachtigall's site substantially meets the requirements of current FDA/ICH GCP standards. Seven minor nonconformities were noted."

On March 20-21, 2006, an internal audit was performed at study site 05 (Phoenix, AZ) for Dr. Barricks. Per the submission, "The audit was conducted in order to investigate compliance with current GCP, Novo Nordisk Policies and Clinical Trial SOPs, local guidelines/requirements and local SOPs." The audit report dated April 30, 2006 indicated that "--- the audit team finds that the clinical trial conducted at Dr. Barrick's site substantially meets the requirements of current FDA/ICH GCP standards. Four minor nonconformities and two remarks were noted."

On December 27, 2007, Novo Nordisk was requested to provide the following information to assist in determining the need for a Division of Scientific Investigation (DSI) audit:

- Number of subjects randomized per center.
- Number of subjects treated per center.
- Number of subjects discontinued per center during weeks 1 through 12 and during weeks 13 through 52.
- Number of protocol violations per center. Identify the nature of the protocol violation in footnote.
- Number of major protocol violations per center. Identify the nature of the major protocol violation in a footnote.

Novo Nordisk responded on January 3, 2008. From the information received, the following two centers were recommended by the reviewer for Division of Scientific Investigation (DSI) audits:

1. Clinical Site # 15, Dr. Lonnie Clayton Harrell
   Metrolina Medical Research
   1700 Abbey Place
   Suite 209
   Charlotte, NC 28209

2. Clinical Site # 30, Dr. Robert Semo (replaced by Dr. William Koltun)
   Medical Center for Clinical Research
   9040 Friars Road
   San Diego, CA 92108

The Good Clinical Practice Branch I of the Division of Scientific Investigations (DSI) conducted an investigation of Clinical Site # 30 (Dr. William Koltun) between March 19 and April1, 2008. The DSI Clinical Inspection Summary, submitted to DRUP on June 5, 2008, indicates that there "were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms." A Form FDA 483, Inspectional Observations, was issued at the close of the inspection." A written response to the Form 483 was submitted by Dr. Koltun on April 21, 2008.

Per the June 5, 2008 DSI letter to Dr. Koltun, the following was emphasized:

1. "You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]. The protocol required eligible subjects to have at least three urogenital symptoms and at least one of them has to be a moderate to severe symptom as identified by the subject during the last week of the screening period. The Urogenital Symptom Questionnaire for subject # (b)(6) at baseline visit documented either "mild" or "none" for each of the subject's urogenital symptoms."

2. "You did not obtain informed consent from subjects in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60]. The IRB approved an amended informed consent form (version 5.0) on 3/2/06. However, this amended informed consent was not signed and dated by subject # (b)(6) who was randomized in the study on (b)(6) ."

3. "You did not maintain adequate records for disposition of the investigational drug [21 CFR 312.62(a)].

    a. Drug accountability records for subject # (b)(6) document that 135 tablets were dispensed to the subject; however, the returned drug log documents a total of 150 tablets.
    b. Drug accountability records for subject # (b)(6) documents that 135 tablets were dispensed to the subject; however, the returned log shows a total of 150 tablets."

DSI acknowledged Dr. Koltun's assurances that corrective actions had been taken to prevent similar findings from occurring in any future studies.

DSI concluded that "data generated for protocol VAG-2195 at this clinical site appear acceptable for use in support of NDA 20-908/013."

The Good Clinical Practice Branch I of the Division of Scientific Investigations (DSI) conducted an investigation of Clinical Site (b) (6) (Dr. Lonnie Harrell) March 24-25, 2008. The DSI Clinical Inspection Summary, submitted to DRUP on June 9, 2008, indicates that there "were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms." DSI concluded that "data generated for protocol VAG-2195 at this clinical site appear acceptable for use in support of NDA 20-908/013."

In general, DSI states that "for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoints captured as specified in the protocol."

4.5 Compliance with Good Clinical Practices

The primary, Phase 3a, safety and efficacy Study VAG-2195 appears to have been conducted in accordance with regulations pertaining to Good Clinical Practice (GCP), the International Conference on Harmonization: Good Clinical Practice Consolidation Guidelines, the Code of Federal Regulations (Notice of Availability, *Federal Register* 25692, May 6, 1997), and the Declaration of Helsinki (revised Hong Kong, 1989).

Written informed consent was obtained before subject enrollment. Each subject was assigned a subject number, which was used on the case report form (CRF) instead of the subject's name.

4.6 Financial Disclosures

Form FDA 3454 (4/06) signed by Mary Ann McElligott, Ph.D., Associate Vice President, Regulatory Affairs is included in the submission. Per the information provided, no clinical investigator disclosed any "propriety interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b)" and "no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)." A list of all investigators for Study VAG-2195 is attached to Form FDA 3454 (4/06).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Systemic bioavailability of the 10 mcg estradiol vaginal tablet was compared to the currently-marketed Vagifem® 25 mcg vaginal tablet. Study VAG-1850 was a randomized, open-label, multiple-dose, single-center (Germany), parallel-group clinical trial that enrolled 58 subjects. Randomized subjects met the following criteria (not inclusive):

- had not received hormone injections in the prior 6 months;
- had not received other hormone therapy for the 3 months prior to treatment;
- had serum E2 < 20 pg/mL and FSH > 40 mIU/mL.

Fifty-eight (58) randomized subjects (mean age 65.2 ± 2.9 years) were assigned to once-daily therapy with either 10 mcg estradiol vaginal tablets (29 subjects) or Vagifem® 25 mcg vaginal tablet (29 subjects) for 2 weeks followed by 10 weeks of twice-weekly therapy. Blood sampling for determination of 24-hour plasma concentration profiles occurred at day -1, day 1 (first dose), day 14-15 (last once-daily dose), day 82 (a no-dose day during twice weekly therapy), and day 83 (final dose of twice-weekly therapy). Estradiol (E2), estrone (E1), and estrone sulfate (E1S), and pharmacokinetics parameters derived from 24-hour concentration profiles included $AUC_{(0\text{-}24)}$, $C_{ave(0\text{-}24)}$, C_{max}, C_{min}, T_{max}.

The primary endpoint in Study VAG-1850 for comparing systemic bioavailability of the two formulations was $AUC_{(0-24)}$ for E2

Per the submission, the 10 mcg estradiol vaginal tablet formulation "demonstrated a pharmacokinetic profile that was generally similar to Vagifem 25 µg, but systemic estrogen exposure was reduced as measured by $AUC_{(0-24)}$ for E2." "The Vagifem 10 µg formulation was associated with consistently lower mean plasma concentrations of E2, E1, and E1S than the Vagifem 25 µg tablet." Per the submission, "there were no subjects with average plasma concentrations of E2, as measured by $C_{ave(0-24)}$, above 20 pg/mL (a threshold of interest selected for the study) during administration of the Vagifem 10 µg tablet, even after 14 days of once daily administration. In the Vagifem 25 µg tablet group, the proportion of subjects having average plasma E2 concentrations of 20 pg/mL or more was 54% at Day 1, but declined to 37% at Day 14, and only 15% after 10 weeks of maintenance therapy (Day 83)."

In Study VAG-1850, 29 subjects received 10 mcg estradiol vaginal tablets and 29 subjects received Vagifem® 25 mcg tablets (total 58 subjects). Fifty-six (56) subjects completed Study Vag-1850 (29 subjects in the 10 mcg estradiol vaginal tablets treatment group [100%] and 27 subjects in the Vagifem® 25 mcg tablets treatment group [93.1%, 27 of 29 subjects]).

5.2 Pharmacodynamics

No pharmacodynamic studies related to efficacy were conducted for the 10 mcg estradiol vaginal tablet.

5.3 Exposure-Response Relationships

An increased incidence of shifts from baseline TVU measurements < 4 mm to > 4 mm was observed in Study VAG-2195 for the 10 mcg estradiol vaginal tablet. These findings are discussed further in Section 7.1.3 "Dropouts and Other Significant Adverse Events" of this review.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Vagifem® (estradiol vaginal tablets) 25 mcg is currently approved for the treatment of atrophic vaginitis.

sNDA 20-908/SE2-013 is seeking approval of the 10 mcg estradiol vaginal tablet (administered intravaginally daily for 2 weeks followed by twice-weekly administration) for the (b)(4)

6.1.1 Methods

The clinical program to evaluate the efficacy and safety of the 10 mcg estradiol vaginal tablet included the single, randomized, double-blind, placebo-controlled, 12-month, Phase 3a Study VAG-2195. Primary, Phase 3a Study VAG-2195 will be discussed further in this review.

6.1.2 General Discussion of Endpoints

The Agency's 2003 draft clinical evaluation Guidance for Industry recommends three co-primary endpoints for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy to address the resulting estrogen deprived changes in the genitourinary tract. In the vulvar area and vagina, the vaginal epithelium becomes dry and atrophic, which causes inflammation, discomfort, itching, and dyspareunia. A lateral wall vaginal cytology smear (allowing the cytological examination of vaginal mucosa epithelial cells) demonstrates an increased proportion of vaginal parabasal epithelial cells and a decreased proportion of vaginal superficial epithelial cells. Vaginal pH increases from the normal 3.5 to 4.0 (a pH which favors lactobacilli) to 6.0 to 8.0 (a pH which favors pathogenic organisms).

Per the Agency's 2003 draft clinical evaluation guidance document, the Agency recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that:

1) have appropriate inclusion and exclusion criteria;
2) conduct appropriate study analyses; and
3) evaluate the following three co-primary endpoints:

- The mean change from baseline to week 12 in the vaginal maturation index (proportion of superficial and parabasal cells). For study inclusion, study participants would have no greater than 5 percent superficial cells on a vaginal smear at baseline. The primary efficacy analysis should show a statistically significant increase in superficial cells and a statistically significant decrease in parabasal cells.

- The mean change from baseline to week 12 in vaginal pH. For study inclusion, study participants should have a vaginal pH > 5.0 at baseline. The primary efficacy analysis should show a statistically significant lowering of vaginal pH.

- The mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. For study inclusion, study participants would have self-identified at least one moderate to severe vulvar and vaginal atrophy symptom. The primary efficacy analysis should show statistically significant improvement in the moderate to severe symptom identified by the

subject as most bothersome. The recommended subject self-assessed symptoms of vulvar and vaginal atrophy include:

1. Vaginal dryness (categorized as none, mild, moderate or severe).
2. Vaginal and/or vulvar irritation/itching (categorized as none, mild, moderate or severe).
3. Vaginal pain associated with sexual activity (categorized as none, mild, moderate or severe).
4. Vaginal bleeding associated with sexual activity (categorized as none, mild, moderate or severe).

The Division of Reproductive and Urologic Products (DRUP) accepts that for number 3 above (vaginal pain associated with sexual activity) and number 4 above (vaginal bleeding associated with sexual activity) that a subject's response might be NA = not applicable because of the absence of sexual activity in the reporting period.

6.1.3 Study Design

The primary objective of Phase 3a Study VAG-2195 was "to evaluate the efficacy of Vagifem 10 µg compared to placebo as assessed by the clinical symptoms and the objective parameters. The secondary objective was to evaluate the endometrial safety from endometrial biopsies taken at the beginning and at the end of study treatment (12 months)."

Per the submission, the primary efficacy endpoints were the mean change from baseline to week 12 in: 1) vaginal Maturation Index and Maturation Value, 2) vaginal pH, and 3) the moderate to severe symptom that was identified by the patient as being most bothersome to her.

Other efficacy endpoints in Study VAG-2195 were vaginal health (the investigator evaluated 5 components: vaginal secretions, epithelial integrity, epithelial surface thickness, vaginal color, and vaginal pH at visits 1, 2, 3, 4, 5, 6, and 9), urethral Maturation Index and urethral Maturation Value, the average score of 3 urogenital symptoms (dryness, soreness and irritation), and the average score of 6 urogenital symptoms (vaginal dryness, vaginal/vulvar irritation, vaginal soreness, pain/burning during urination [dysuria], pain associated with sexual activity [dyspareunia], vaginal bleeding associated with sexual activity).

The key safety endpoint in Study VAG-2195 was the "evaluation of the hyperplasia rate (determined through endometrial biopsies) at the end of study (12 months). Other safety endpoints included:

- Vital signs (weight, height, heart rate, systolic and diastolic blood pressure)
- Physical examination (ears, eyes, nose, throat, neck), respiratory, cardiovascular, gastrointestinal, musculoskeletal, central and peripheral nervous system, and skin
- Gynaecological examination
- Papanicolaou cervical smear

- Transvaginal ultrasound
- Adverse events

Inclusion criteria utilized in Study VAG-2195 included, but were not limited to, "patients should have at least three urogenital symptoms and at least one of them has to be a moderate to severe symptom as identified by the patient --- during the last week of the screening period, 5% superficial cells as assessed by evaluation of vaginal cytology, vaginal pH > 5, endometrial thickness < 4.0 mm (double layer), as measured by transvaginal ultrasound." Exclusion criteria included, but were not limited to, "endometrial hyperplasia diagnosed during the screening period, and abnormal genital bleeding of unknown etiology."

Medical Officer's Comments:

Overall, the inclusion and exclusion criteria utilized in Phase 3a Study VAG-2195 were appropriate. See the final protocol for Study VAG-2195 for a full listing of inclusion and exclusion criteria.

Subjects were free to withdraw from Study VAG-2195 at any time. If a subject was judged non-compliant with procedures or presented a safety concern, she was withdrawn from the clinical trial. Per the protocol, all of the assessments require at the end-of study were performed when a subject was withdrawn. The reasons for withdrawal were to be documented in the case report form. Withdrawn subjects were not replaced.

In Study VAG-2195, subjects were randomized in a 2:1 ratio and received either 10 mcg estradiol vaginal tablet or placebo vaginal tablet. Randomization was carried out centrally using a telephone randomization system (IVRS: Interactive Voice Response System).

Per the protocol for Study VAG-2195, no vaginal lubricants were to be used prior to the week 12 assessment. The use of a vaginal lubricant supplied by Novo Nordisk was permitted for relief of symptoms following the week 12 assessment through the end of the study (week 52).

All study materials, including the vaginal lubricant, were supplied by Novo Nordisk A/S, Denmark and labeled according to regulations. Manufacturing information for the estradiol and placebo vaginal tablets follows:

Trial Product	Dose	Batch Number	Expiry Date
Estradiol vaginal tablet	10 mcg	SBBE044	01-Jun-2008
		PBBM111	28-Sept- 2006
Placebo vaginal tablet	——	MBBO006	18-Mar-2007
		SBBD058	07-July-2011

Subjects were seen a total of 9 times in Study VAG-2195: screening (visit 1 at 2-3 weeks prior to randomization), baseline (visit 2 at week 0), and visits 3 (week 2 ± 3 days), 4 (week 4 ± 5 days),

5 (week 8 ± 7 days), 6 (week 12 ± 7 days), 7 (week 26 ± 10 days), 8 (week 39 ± 10 days), and 9 (week 52 ± 14 days).

Vaginal Maturation Index:

Vaginal smears taken from the upper third of the right vaginal wall were obtained at visits 1 (2-3 weeks prior to randomization), 2 (baseline), 3, 4, 5, 6 and 9 (week 52) and sent to a central laboratory for evaluation. Urethral smears were obtained from the distal one third of the urethra with the same degree of frequency. The number of parabasal, intermediate, and superficial cells (Maturation Index) were counted twice and the mean is given for each cell type. The proportion of parabasal, intermediate, and superficial cells are presented as percentages. In addition, a Maturation Value was calculated by multiplying the percentages of the cell type per the following equation:

Maturation Value = 0 x (parabasal cells, %) + 0.5 x (intermediate cells, %) + 1.0 x (superficial cells, %).

Medical Officer's Comments:

The Maturation Value is a weighted average of the Maturation Index. For the purpose of demonstrating effectiveness of the drug product, only the mean change in the proportion (percentage) of superficial and parabasal cells will be considered. As previously noted, the mean change from baseline to week 12 in the proportion of superficial and parabasal cells is a recommended co-primary endpoint for a VVA indication.

Vaginal pH:

A vaginal pH score was assessed at visits 1, 2, 3, 4, 5, 6 and 9 and recorded and scored within four intervals (pH < 5 [no atrophy] x 0, pH of 5-5.49 [mild atrophy] x1, pH of 5.5-6.49 [moderate atrophy] x 2, and pH of > 6.49 [severe atrophy] x 3). The use of a vaginal pH score was specified in the study protocol.

Medical Officer's Comments:

A DRUP letter to the Applicant, dated February 19, 2008, identified the following potential review issue:

"Per the Agency's 2003 draft clinical evaluation Guidance for Industry, the mean change in vaginal pH between baseline and week 12 is one of three recommended co-primary endpoints for demonstrating effectiveness in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy. You have not provided an analysis of mean change in vaginal pH between baseline and week 12 as one of the three recommended co-primary endpoints. The submitted mean change calculation based on a calculated vaginal pH score between baseline and week 12 is not acceptable. Provide an analysis of mean change in vaginal pH between baseline and week 12 based on the observed pH values at each time point."

The Applicant responded on April 18, 2008 indicating the following:

"In the VAG-2195 study, pH measurements were obtained using pH strips. Using pH strips to measure vaginal pH is a well accepted method in clinical practice for the diagnosis of vaginal atrophy along with physical examination. During the screening visit, to select subjects with a vaginal pH > 5.0 (one of the specific inclusion criteria), the observed reading of the vaginal pH test strip were recorded as values in the case report form per the VAG-2195 protocol. For the baseline and treatment visits, the observed vaginal pH values were uniformly recorded within four intervals, as a score (not a calculated value), corresponding to pH < 5 = 0 (no atrophy), pH 5-5.49 = 1 (mild atrophy), pH 5.5-6.49 = 2 (moderate atrophy), or pH > 6.49 = 3 (severe atrophy) as stated in the protocol. The observed pH values were not captured on the case report forms or on the source documents during the baseline and treatment visits and thus it is not possible to retrospectively collect this information from the sites." "The mean change from baseline to week 12 in pH, a defined protocol efficacy component, was therefore based on the observed pH values which were captured as a score."

Regarding the approval of Vagifem® 25 mcg (b)(4)*, the Applicant stated: "In the VAG/PD/9/USA study, measuring vaginal pH and recording it in the four intervals as stated above was also the approach. The VAG/PG/9/USA study was submitted to NDA 20-908 and was accepted by the Division for approval of Vagifem 25 mcg tablets. This precedence was a key consideration when the VAG-2195 protocol was written because it was considered important to be able to reflect upon the experience of the 25 mcg product to bring a lower dose 10 mcg product to market."*

"The Division's first feedback on VAG-2195 in response to IND Serial No. 052 was received on February 1, 2008. While the response made specific reference to including mean change from baseline to week 12 in vaginal pH as one of three equal co-primary endpoints, as per the Agency's 2003 Guidance, the Division did not comment on the method of collecting or recording the observed vaginal pH as a score rather than a value, and accordingly, no changes were considered necessary. The case report forms were therefore designed to capture the observed vaginal pH in the four stated intervals as per the VAG-2195 protocol. Based on the above information, it is not possible for the sponsor to fulfill the Agency's request to provide an analysis of mean change in vaginal pH between baseline and week 12 based on the observed pH value at each time point"

Because of the Applicant's explanation as stated above, the reviewer concurs with the use of a vaginal pH score with the understanding that a pH of < 5 received a score of zero, a pH within the interval of 5 – 5.49 received a score of 1, a pH within the interval of 5.5 – 6.49 received a score of 2, and a pH reading of > 6.49 received a score of 3.

Vulvar and Vaginal Atrophy Symptom Assessment:

Subjects were asked to complete an independent self-administered questionnaire describing the symptoms they experienced and the severity at visit 1, 2, 3, 4, 5, 6, 7, 8 and 9. Subjects were

instructed to identify the one vaginal symptom that was most bothersome to her at visit 2 (baseline), visit 6 (week 12) and at end-of-study (visit 9 [week 52] or early termination). The following definitions were used to assess the severity of symptoms:

Vaginal dryness:

None:	I do not have vaginal dryness.
Mild:	I occasionally feel dryness, but it does not interfere with my daily activities.
Moderate:	I feel a sensation of dryness most of the time, however, the dryness does not interfere with my daily activities.
Severe:	I feel a sensation of dryness most of the time. Dryness interferes with my daily activity.

Vaginal and/or vulvar irritation/itching:

None:	I do not have vaginal and/or vulvar irritation/itching.
Mild:	I occasionally feel irritation/itching, but the irritation/itching does not interfere with my daily activities.
Moderate:	I feel a sensation of irritation/itching most of the time, however, the irritation/itching does not interfere with my daily activities.
Severe:	I feel a sensation of irritation/itching most of the time. Irritation/itching interferes with my daily activity.

Vaginal soreness:

None:	I do not have vaginal soreness.
Mild:	I occasionally feel soreness, however the soreness does not interfere with my daily activities.
Moderate:	I feel a sensation of soreness most of the time, however, the soreness does not interfere with my daily activities.
Severe:	I feel a sensation of soreness most of the time. Soreness interferes with my daily activity.

Pain or burning during urination (dysuria):

None:	I do not experience pain or burning during urination.
Mild:	I feel pain or burning during urination occasionally, however, it does not interfere with my daily activities.
Moderate:	I feel pain or burning during urination most of the time, however, the pain or burning does not interfere with my daily activities.
Severe:	I feel pain or burning during urination most of the time. Pain or burning during urination interferes with my daily activity.

Vaginal pain associated with sexual activity/during intercourse (dyspareunia):

N/A:	I am not sexually active.
None:	I do not feel vaginal pain or soreness during sexual intercourse.
Mild:	I feel vaginal pain sometimes during sexual intercourse. Occasionally I must stop during the sex act, due to pain.

Moderate: I feel significant vaginal pain most of the time during sexual intercourse which often interferes with sexual enjoyment. I often stop during the sex act, due to pain.
Severe: I feel significant vaginal pain most of the time during sexual intercourse. I cannot enjoy intercourse and I often must stop during the sex act, due to pain. I avoid intercourse because of the vaginal pain (dyspareunia) during the sex act.

Vaginal bleeding associated with sexual activity;
N/A: I am not sexually active.
None: I have no vaginal bleeding during sexual intercourse.
Mild: I have vaginal bleeding during sexual intercourse occasionally but it does not stain my clothing and I never need to wear a pad or tampon.
Moderate: I have vaginal bleeding during sexual intercourse occasionally which stains my clothing or sometimes requires wearing a pad or tampon.
Severe: I have vaginal bleeding during sexual intercourse most of the time which stains my clothing, and I always need to wear a pad or tampon after sex.

The presence and severity of each recorded symptom and physical sign were coded as follows: none = 0, mild = 1, moderate = 2, severe = 3 and documented in the CRF.

Vaginal Health Assessment:

Investigators examined and graded vaginal health at visits 2 (baseline), 3 (week 2), 4 (week 4), 5 (week 8), 6 (week 12), 7 (week 26), 8 (week 39), and 9 (week 52). The following observations were made and the severity of the observed conditions was defined as follows:

- Vaginal secretions:
  No atrophy: Normal, clear secretions noted on vaginal walls
  Mild: Superficial coating of secretions, difficulty with speculum insertion
  Moderate: Scant and not covering entire vaginal vault, may need lubrication with speculum insertion to prevent pain
  Severe: None, inflamed, ulceration noted, need lubrication with speculum insertion to prevent pain

- Vaginal epithelial integrity:
  No atrophy: Normal
  Mild: Vaginal surface bleeds with scraping
  Moderate: Vaginal surface bleeds with light contact
  Severe: Vaginal surface has petechiae before contact and bleeds with light contact

- Vaginal epithelial surface thickness:
  No atrophy: Rugation and elasticity of vault
  Mild: Poor rugation with some elasticity noted of vaginal vault
  Moderate: Smooth, some elasticity of vaginal vault

Severe: Smooth, no elasticity, constricts in upper 1/3 of vagina or loss of vaginal tone (cystocele and/or rectoceles)

- Vaginal color:
  No atrophy: Pink
  Mild; Lighter in color
  Moderate: Pale in color
  Severe: Transparent, either no color or inflamed

- Vaginal pH:
  No atrophy: < 5
  Mild: 5 – 5.49
  Moderate: 5.5 – 6.49
  Severe: > 6.49

Statistical and Analytical Plans:

No interim analyses were conducted in 52-week Study VAG-2195.

Per the submission, efficacy analyses were performed on the Intent-to-Treat (ITT) population using last observation carried forward (LOCF). Conclusions regarding treatment benefits were drawn against comparisons made with placebo over the initial 12-week double-blind treatment period. Analysis of covariance (ANCOVA) was used for the between group comparison in analyzing the symptom data with treatment as a fixed effect and corresponding baseline value as a covariate. The ANCOVA model was also used to analyze the vaginal Maturation Index, Maturation Value, and vaginal pH. Week 12 efficacy data was analyzed in two ways: 1) the subjects with observations at week 12, and 2) applying the LOCF method for subjects who withdrew and had post-treatment values. No adjustments for site interaction or multiple comparisons were made.

In protocol amendment number 2 dated February 3, 2006, the total number of subjects to be enrolled in Phase 3a Study VAG-2195 was reduced from 600 subjects (400 subjects treated with 10 mcg estradiol vaginal tablets and 200 subjects treated with placebo vaginal tablets) to 300 subjects (200 subjects treated with 10 mcg estradiol vaginal tablets and 100 subjects treated with placebo vaginal tablets) due to "slow patient enrollment". Per the submission, however, a sample size of 200 subjects treated with 10 mcg estradiol vaginal tablets and 100 subjects treated with placebo vaginal tablets would provide "90% power to detect a difference of 0.48 in change from baseline to Week 12 for the relief of urogenital symptoms (based on the most bothersome symptom score of dryness, irritation/itching, soreness, dysuria, pain associated with sexual activity, and bleeding associated with sexual activity), with an estimated standard deviation of 1.1 in change from baseline to 12 weeks." The sample size would provide "90% power to detect a difference of 7.2% with estimated standard deviation 16.5% in change from baseline to 12-week score for vaginal cytology ─ Parabasal Cell (%) and to detect a difference of 8.6% with estimated standard deviation 19.7% in change from baseline to 12-week score for vaginal cytology ─ Superficial Cell (%)." For vaginal pH, the sample size would provide "90% power to

detect a difference of 0.44 with estimated standard deviation 1.0 in change from baseline to 12 weeks." Per the submission, this estimated sample size was based on a 2-sided significance level of 0.05 and included a 15% dropout rate.

6.1.4 Efficacy Findings

The primary objective of Study VAG-2195 was "to evaluate the efficacy of Vagifem 10 µg compared to placebo as assessed by the clinical symptoms and the objective parameters." Per the submission, the "objective parameters" included vaginal and urethral cytology, Maturation Value, and grading of vaginal health. The most bothersome urogenital symptoms were classified as subjective evaluations. "The secondary objective was to evaluate the endometrial safety from endometrial biopsies taken at the beginning and at the end of study treatment (12 months)."

Per the submission, the primary efficacy endpoints were the mean change from baseline to week 12 in: 1) vaginal Maturation Index and Maturation Value, 2) vaginal pH, and 3) the moderate to severe symptom that was identified by the patient as being most bothersome to her.

Other efficacy endpoints in Study VAG-2195 were vaginal health (the investigator evaluated 5 components: vaginal secretions, epithelial integrity, epithelial surface thickness, vaginal color, and vaginal pH at visits 1, 2, 3, 4, 5, 6, and 9), urethral Maturation Index and urethral Maturation Value, the average score of 3 urogenital symptoms (dryness, soreness and irritation), and the average score of 6 urogenital symptoms (vaginal dryness, vaginal/vulvar irritation, vaginal soreness, pain/burning during urination [dysuria], pain associated with sexual activity [dyspareunia], vaginal bleeding associated with sexual activity).

Disposition of Subjects:

In Phase 3a Study VAG-2195, a total of 309 subjects were randomized. One subjects randomized to the placebo treatment group did not use study medication. Therefore, a total of 308 subjects who applied study medication at least once make up the safety population in this submission. Of the 309 randomized subjects, 234 (76%, 234 of 309 randomized subjects; 164 subjects [80.0%] in the 10 mcg estradiol vaginal tablet treatment group and 70 subjects [67.3%] in the placebo vaginal tablet treatment group) completed 52-week Study VAG-2195. Seventy-five (75) subjects discontinued Study VAG-2195 before week 52 (24%, 75 of 309 randomized subjects). The general reasons for discontinuing Study VAG-2195 are listed in Table 2.

Table 2**:** Dispositions of Subjects in Study VAG-2195

	Placebo Vaginal Tablet n (%)	**10 mcg Estradiol Vaginal Tablet n (%)**	**Total n (%)**
Number of subjects randomized	104	205	309
Number of subjects completed	70 (67.3)	164 (80.0)	234 (75.7)
Number of subjects discontinued	34 (32.7)	41 (20.0)	75 (24.3)
Reasons for discontinuation			
Adverse event	5 (4.8)	11 (5.4)	16 (5.2)

Protocol non-compliance	2 (1.9)	6 (2.9)	8 (2.6)
Ineffective therapy	11 (10.6)	6 (2.9)	17 (5.5)
Other	16 (15.4)	18 (8.8)	34 (11.0)

Source: sNDA 20-908/SE2-013, Clinical Trial Report, Table 10-1 Disposition of Patients, page 48 of 1507 and Selected Data Listing 16.2.1-2.

Of the 75 subjects who discontinued Study VAG-2195, 16 subjects (5.2%, 16 of 309 randomized subjects) discontinued due to adverse events, 17 subjects discontinued because of ineffective therapy (5.5%, 17 of 309 randomized subjects), while 11% of subjects (34 of 309 randomized subjects) discontinued due to "Other" which includes: personal issues, withdrew consent, lost to follow-up, and protocol violations.

Medical Reviewer's Comments:

Overall, the percentage of subjects discontinuing Study VAG-2195 (24%, 75 of 309 randomized subjects) is not unexpected for a 52-week placebo-controlled clinical trial. Discontinuations due to adverse events were similar between the two treatment groups (5.4%, 11 of 205 randomized subjects) in the 10 mcg estradiol vaginal tablet treatment group and 4.8% (5 of 104 randomized subjects) in the placebo vaginal tablet treatment group. However, discontinuations due to ineffective therapy was significantly higher in the placebo vaginal tablet treatment group (10.6%, 11 of 104 randomized subjects) than in the 10 mcg estradiol vaginal tablet treatment group (2.9%, 6 of 205 randomized subjects), even though the protocol allowed the use of vaginal lubricant (study supplied) in both treatment groups after week 12. In addition, near twice as many subjects in the placebo vaginal tablet treatment group (15.4%, 16 of 104 randomized subjects) as compared with the 10 mcg estradiol vaginal tablet treatment group (8.8%, 18 of 205 randomized subjects) discontinued due to "Other".

Thirty-three (33) subjects (10.7%, 33 of 309 randomized subjects) had protocol deviations that involved at least one inclusion or exclusion criteria. The following subjects failed to meet at least one of the inclusion criteria:

- Inclusion criterion # 4 (serum FSH level > 40 mIU/mL and estradiol < 20 pg/mL) = Subject (b)(6)
- Inclusion criterion # 5 (subject should have at least 3 urogenital symptoms and at least one of them has to be a moderate to severe symptom as identified by the subject during the last week of the screening period) = Subjects (b)(6)
- Inclusion criterion # 6 (5% superficial cells as assessed by evaluation of vaginal cytology) = Subjects (b)(6)
- Inclusion criterion # 7 (vaginal pH > 5) = Subjects (b)(6)
- Inclusion criterion # 8 (endometrial thickness < 4.0 mm (double layer), as measured by TVU = Subjects (b)(6)
- Inclusion criterion # 9 (normal mammogram within 6 months prior to trial start (visit 1) or normal mammogram prior to visit 2 = Subjects (b)(6)

The following subjects met at least one of the exclusion criteria:

- Exclusion criterion # 4 (endometrial hyperplasia diagnosed during the screening period) = Subject (b)(6)
- Exclusion criterion # 7 (use of any type of vaginal or vulvar preparations 1 month prior to visit 2 - (b)(6)
- Exclusion criterion # 9 (known insulin dependent or non-insulin dependent diabetes mellitus) = Subject (b)(6)
- Exclusion criterion # 10 (systolic blood pressure 160 mm Hg and/or diastolic blood pressure 100 mm Hg, currently treated or untreated = Subject (b)(6)
- Exclusion criterion # 15 (body mass index > 35.0 kg/m = Subjects (b)(6)
- Exclusion criterion # 16 (Papanicolaou cervical smear presenting with ASCUS or neoplastic changes = Subjects (b)(6)
- Exclusion criterion # 17 (known or suspected vaginal infection requiring further treatment) = Subjects (b)(6)

Medical Officer's Comments:

A number of deviations involved subjects who failed to meet 2 of the recommended inclusion criteria needed to demonstrate VVA efficacy endpoints, namely, study participants would have no greater than 5 percent superficial cells on a vaginal smear at baseline and study participants should have a vaginal pH > 5.0 at baseline. As shown above, 6 subjects had > 5% superficial cells on the screening vaginal epithelial smear and 3 subjects had a vaginal pH of ≤ 5. Therefore, these subjects would not be eligible for inclusion in analyses of the subjects who met the following criteria at baseline: no greater than 5 percent superficial cells on a vaginal smear, a vaginal pH > 5.0, and a moderate to severe most bothersome vaginal symptom with a severity score of 2 or greater.

However, the largest majority of inclusion criteria deviations involved subjects with a screening TVU > 4 mm (12 subjects). Endometrial thickness is discussed further in Subsection 7.1.3.3 "Other significant adverse events". No safety issues arise from these protocol deviations.

Per the submission, 35 subjects (11.3%, 35 of 309 randomized subjects) had general procedure deviations during the conduct of Study VAG-2195. A summary of general procedural deviations is shown in Table 3.

Table 3: Number of Subjects with General Procedure Deviations

Procedure Deviation	**Subject Number** (b)(6)
Pap smear not done	
Blood sample not processed/processed correctly/drawn out of window	
Visit out of window	
Final ultrasound not done	
Procedure done out of window/not done	
Dosing error	
No mammograms	
No repeat endometrial biopsy a visit 9	

	(b)(6)
Subject randomized without repeat endometrial biopsy	
Continue in trial after missing 7 doses	
No end of trial visit	
Randomization error	
Source document for end of trial physical/pelvic exam	

Source: sNDA 20-908/SE2-013 Clinical Trial Report, Table 9-3, page 46 of 1507.

Medical Officer's Comments:

As shown in Table 3, several of the reported procedure deviations resulted in the absence of specific safety evaluations, namely, no mammogram performed (1 subject), no evaluable screening endometrial biopsy (4 subjects), absence of end-of-study endometrial biopsy (2 subjects) or TVU (1 subject), and no end-of-study visit (5 subjects).

The following table shows the demographic characteristics for the randomized population in Phase 3a Study VAG-2195.

Table 4**:** Subject Demographics and Baseline Characteristics: Study VAG-2195

Characteristic	**Placebo Vaginal Tablet n = 104**	**Estradiol Vaginal Tablet n = 2.5**	**Total n = 309**
Mean Age (SD), years	57.5 (5.27)	57.5 (5.64)	57.6 (5.51)
Range	46 – 75	46 – 81	46 – 81
Race, n (%)			
White	95 (91.3)	192 (93.7)	287 (92.9)
Black or African American	4 (3.8)	6 (2.9)	10 (3.2)
Asian	3 (2.9)	2 (1.0)	5 (1.6)
American Indian or Alaskan Native	0	2 (1.0)	2 (0.6)
Native Hawaiian or Pacific Islander	0	1 (0.5)	1 (0.3)
Other	2 (1.9)	2 (1.0)	4 (1.3)
Body Weight, kg			
Mean (SD)	66.2 (12.0)	66.3 (10.5)	66.2 (11.0)
Range	45.8 – 99.6	40.8 – 95.3	40.8 – 99.6
Body Mass index, kg/m^2			
Mean (SD)	24.9 (4.3)	25.2 (3.5)	25.1 (3.8)
Range	18.0 – 35.0	17.9 – 35.3	17.9 – 35.3
Time since last menses			
Mean (SD)	8.2 (5.3)	8.0 (5.8)	8.1 (5.7)
Range, n (%)	1 -29	1 – 32	1 – 32
< 2	1 (1.0)	2 (1.0)	3 (1.0)
2 to < 5	35 (33.7)	81 (39.5)	116 (37.5)
6 to < 10	33 (31.7)	65 (31.7)	98 (31.7)
≥ 10	35 (33.7)	57 (27.8)	92 (29.8)

Source: sNDA 20-908/SE2-013, Table 3-1 Subject Demographics and Baseline Characteristics, page 11 of 40 and Clinical Trial Report, Table 11-3, page 52 of 1507.

Table 5 shows the demographic characteristics for the randomized population in Phase 1 Study VAG-1850.

Table 5**:** Subject Demographics and Baseline Characteristics in Study VAG-1850

Characteristic	**10 mcg Estradiol Vaginal Tablet (n = 29)**	**Vagifem® 25 mcg (n = 28)**
Age (years) Mean (SD) [Range]	65.4 (2.6) [60 – 70]	65.1 (3.2) [60 – 70]
Race (n, %) White	29 (100%)	28 (100%)
Weight (kg) Mean (SD) [Range]	65.2 (9.1) [47.6 – 84]	67.3 (10.3) [53.7 -97]
BMI (kg/m^2) Mean (SD) [Range]	24.9 (3.1) [18.5 – 29.9]	25.2 (3.0) [19.8 -30]
Hysterectomy (n) Y/N	0/29	0/28

Source: sNDA 20-908/SE2-013, Summary of Clinical Safety Studies, Table 1-6, page 10 of 46.
Definitions: SD = Standard Deviation.

Medical Officer's Comments:

There were no statistically significant differences among treatment groups for any demographic characteristic in both Study VAG-2195 and VAG-1850. However, the majority of subject in both studies were White (92.9%, 287 of 309 subjects in Study Vag-2195 and 100%, 57 of 57 subjects in Study VAG-1850). African American, Asian, or other races were severely underrepresented.

Overall, the mean age of subjects across treatment groups in Phase 1 Study VAG-1850 (mean age 65.2 [SD = 2.9]) was higher than subjects in Phase 3a Study VAG-2195 (mean age 57.6 [5.51]). These age differences in study populations across the two studies in this submission do not raise safety issues.

Measurement of Treatment Compliance:

Per the protocol submitted for Study VAG-2195, subject compliance was assessed at visits 3 (week 2), 4 (week 4), 5 (week 8), 6 (week 12), 7 (week 26), 8 (week 39) and 9 (week 52) through interviews and the number of applicators and tablets returned at each of these visits. A subject was considered non-compliant if she missed more than 7 days of study medication at any specific month or more than 20% of the study medication for the full 52 weeks of Study VAG-2195.

Table 6 shows the number of subjects meeting these criteria.

Table 6: Summary of Compliance – Safety Population in Study VAG-2195

Visit	**Treatment**	**Missed 7 Days of Treatment Since Last Visit**		**Used any Type of Prohibited Vaginal or Vulvar Preparation Since Last Visit**		**Used Vaginal Lubricant Provided for Use Following Week 12**		**Missed 20% of Total Treatment**	
		Yes	No	Yes	No	Yes	No	Yes	No
Week 2	Placebo (n = 103)	0	99	1	98	-	-	-	-

	Estradiol 10 mcg (n = 205	1	196	1	196	-	-	-	-
Week 4	Placebo (n = 103)	1	95	0	96	-	-	-	-
	Estradiol 10 mcg (n = 205	0	197	5	192	-	-	-	-
Week 8	Placebo (n = 103)	0	89	3	86	-	-	-	-
	Estradiol 10 mcg (n = 205	0	193	1	192	-	-	-	-
Week 12	Placebo (n = 103)	0	83	0	83	-	-	-	-
	Estradiol 10 mcg (n = 205	3	182	2	183	-	-	-	-
Week 26	Placebo (n = 103)	3	75	1	77	30	48	-	-
	Estradiol 10 mcg (n = 205	8	171	4	175	84	95	-	-
Week 39	Placebo (n = 103)	3	71	1	71	35	17	-	-
	Estradiol 10 mcg (n = 205	2	166	5	163	82	86	-	-
Week 52 or EOT	Placebo (n = 103)	7	85	1	91	38	53	3	89
	Estradiol 10 mcg (n = 205	25	170	4	191	87	107	18	177

Source: sNDA 20-908/SE2-013, Final Study Report, Selected Data Listing 16.2.5-1, page 441 of 1507.

Medical Officer's Comments:

At week 12, 89% of subjects in the 10 mcg estradiol vaginal tablet treatment group (182 of 205 treated subjects) and 80% of subjects in the placebo vaginal tablet treatment group (83 of 103 treated subjects) met defined compliance. Similar percentages are shown at week 52 (83% for the 10 mcg estradiol vaginal tablet treatment group [170 of 205 treated subjects] and 82% for the placebo vaginal tablet treatment group [85 of 103 treated subjects]). Overall, the majority of subjects in Phase 3a Study VAG-2195 (86% in both treatments groups) were compliant during the 52 weeks of treatment.

From Table 6 we see that more subjects in the 10 mcg estradiol vaginal tablet treatment group as compared with the placebo vaginal tablet treatment group used vaginal lubricant between weeks 13 to 52. At week 26, a total of 88 subjects in the 10 mcg estradiol vaginal tablet treatment group (43%, 88 of 205 treated subjects) as compared with a total of 31 subjects in the placebo vaginal tablet treatment group (30 %, 31 of 103 treated subjects) used either the study

supplied lubricant or another type of prohibited lubricant. A similar finding was reported at week 52 (44% [91 of 205 treated subjects] in the 10 mcg estradiol vaginal tablet treatment group and 38% [39 of 103 treated subjects] in the placebo vaginal tablet treatment group).

The finding reported in the placebo vaginal tablet treatment group (30% using vaginal lubricant at week 26 and 38% using vaginal lubricant at week 52) is not unexpected in a 52-week placebo-controlled study of postmenopausal women with symptoms of vulvar and vaginal atrophy. The finding reported in the 10 mcg estradiol vaginal tablet treatment group (43% using vaginal lubricant at week 26 and 44% using vaginal lubricant at week 52) is unexpected and unexplained, however.

Table 6 also shows that more subjects in the 10 mcg estradiol vaginal tablet treatment group than in the placebo vaginal tablet treatment group missed 20% of total treatment across the 52-week study or by the time of early termination (8.8%, 18 of 205 treated subjects versus 2.9%, 3 0f 103 treated subjects, respectively. This reported finding is unexplained.

Data Quality Assurance:

To ensure that the data collected were accurate, consistent, complete and reliable; three internal audits were conducted during the conduct of Phase 3a Study VAG-2195. The internal audit performed at Novo Nordisk, Inc in New Jersey on February 2, 2006 reported that "the clinical trial conducted at Novo Nordisk Inc. substantially meets the requirements of current FDA/ICH GCP standards". The internal audits performed at study sites 05 and 46 reported that the clinical trials conducted at these two sites substantially met the requirements of current FDA/ICH GCP standards.

Populations Analyzed:

Per the submission, efficacy analyses were performed in the Intent-to-Treat (ITT) population, which the study protocol defined as all randomized subjects who received at least one dose of study medication and had baseline and one post-baseline efficacy evaluation. For the purpose of this review, the reviewer defines this population as the modified Intent-to-Treat (mITT) population.

In Study VAG-2195, 309 subjects were randomized. Subject (b)(6) did not use study medication and was excluded from the safety population. Subject (b)(6) was "randomized in error". She was discontinued by the Applicant after receiving one day of study medication because "this subject did not meet inclusion criteria no. 6 "Does This Subject Have Less Than Or Equal To 5% Superficial Cells As Assessed By Evaluation Of Vaginal Cytology". Subject (b)(6) did not have a post-baseline efficacy evaluation. Therefore, per the submission defined ITT population, 306 subjects (99.0%, 99 of 309 randomized subjects) received at least one dose of study medication and had a baseline and one post-baseline efficacy evaluation.

On December 27, 2007, the Applicant was requested to provide the following information:

- "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in the percentage of superficial and parabasal cells for the 10 mcg Vagifem and placebo treatment groups (ITT population with LOCF)."

- "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in vaginal pH (ITT population with LOCF)."

- "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in the most bothersome moderate to severe vulvar and vaginal atrophy symptom for each symptom included in the subject self-assessment questionnaire (dryness, irritation, soreness, dysuria, dyspareunia, and bleeding with sexual activity). Include only those subjects who scored the individual symptom as moderate to severe (not mild) and identified the symptom as most bothersome at baseline."

Medical Officer's Comments:

The reviewer considers the analyses requested as a subset of the mITT population.

The designation, mITT-1, will be used in this review to identify those randomized subjects who:

- *received at least one dose of study medication,*
- *had a baseline evaluation, and*
- *had one post-baseline efficacy evaluation;*

who at baseline had;

- *less than or equal to 5% superficial cells on a vaginal smear,*
- *a pH greater than 5, and*
- *self-identified at least one moderate to severe most bothersome symptom*

The Applicant provided the requested information on January 25, 2008 and again on April 17, 2008. The Applicant refers to the requested information as the "Revised ITT population based on FDA criteria". This information will be discussed further in this review.

Per the submission, a confirmatory efficacy analysis was also conducted on the Per Protocol (PP) population, which was comprised of 196 subjects (63.4%, 196 of 309 randomized subjects) with no significant deviations from the study protocol. See Table 7.

Table 7: Analysis Population Sets

Population Sets	10 mcg Estradiol Vaginal Tablet	Placebo Vaginal Tablet	Total
Number of subjects randomized	205	104	309
Safety population (%)	205 (100.0)	103 (99.0)[a]	308 (99.7)
Efficacy population (%)	204 (99.5)[b]	102 (98.1)[c]	306 (99.0)
Intent-to-treat (%)	204 (99.5)	102 (98.1)	306 (99.0)
Per protocol (%)	135 (65.9)	61 (58.7)	196 (63.4)

Source: sNDA 20-908/SE2-013, Final Clinical Study Report, Table 11-1, page 50 of 1507.
Definitions:
Intent-to-treat = All randomized subjects who received at least one dose of study medication and had baseline and one post-baseline efficacy evaluation.
Per protocol = Excludes all subjects who had protocol violations or deviations.
a. Subject 3204 did not receive study medication.
b. Subject 201 was "randomized in error".
c. Subject 2601 withdrew consent and did not have post-baseline data for primary efficacy endpoints.

A total of 110 subjects (35.6%, 110 of 309 randomized subjects) had protocol violations or deviations and were exclude from the per protocol population. The number of subjects and reasons for exclusion are shown in Table 8.

Table 8: Reasons for Exclusion from Per Protocol Population in Study VAG-2195

Reasons for Exclusion	10 mcg Estradiol n (%)	Placebo n (%)	Total n (%)
Total number of subjects excluded	69 (33.7)	41 (39.4)	110 (35.6)
Non-compliance with study drug administration	36 (17.6)	14 (13.5)	50 (16.2)
Most bothersome symptom missing or not moderate/severe at baseline	20 (9.8)	13 (12.5)	33 (10.7%)
Did not complete at least 12 weeks	13 (6.3)	15 (14.4)	28 (9.1)
Inclusion/exclusion criteria violation	20 (9.8)	10 (9.6)	30 (9.7)

Source: sNDA 210908/SE2-013, Final Clinical Trial Report, Table 11-2, page 51 of 1507.

Medical Officer's Comments:

As shown in Table 8, 110 subjects (35.6%, 110 of 309 randomized subjects) were excluded from the PP population. Non-compliance with regards to study drug administration (daily for 2 weeks then twice weekly thereafter) was the most common reason for the exclusion (16.2%, 50 of 309 randomized subjects). A subject was considered non-compliant if she missed more than 7 days of study medication at any specific month or more than 20% of the study medication for the full 52 weeks of Study VAG-2195.

In addition, 10.7% of study subjects (33 of 309 randomized subjects) did not identify a most bothersome symptom or did not indicate that their most bothersome symptom was moderate or severe. A moderate to severe and most bothersome vaginal symptom is one of the specific inclusion criteria recommended for a VVA indication.

Vaginal Maturation Index:

Per the original sNDA 20-908/SE2-013 submission, "12 weeks of local administration of Vagifem 10 μg, induces vaginal epithelial maturation, shifting the atrophic epithelium from a predominantly parabasal cell population to a superficial cell population, which is more typical of pre-menopausal women." "In study VAG-2195, parabasal cells comprised over 40% of the total numbers of cells at baseline, a clear indicator of vaginal epithelial atrophy." "Evaluations of the numbers of parabasal cells indicate that the mean change from baseline to Week 12 (LOCF) for the Vagifem 10 μg was -37.0% ($p< 0.001$, compared to placebo)."

The sNDA submission also reported that at baseline "the proportion of superficial cells was < 5%. The mean change from baseline to Week 12 (LOCF) was approximately 13% ($p< 0.001$, compared to placebo)."

These reported results are shown below:

Mean change from baseline (SD) in the percent of parabasal cells:

Treatment Group	Week 2	Week 4	Week 8	Week 12 (LOCF)
10 mcg estradiol vaginal tablet	-39.3 (40.94)	-38.8 (41.60)	-39.0 (42.12)	-37.0 (43.97)
Placebo vaginal tablet	-11.2 (44.51)	-12.9 (48.46)	-13.7 (44.82)	-9.3 (41.75)

Mean change from baseline (SD) in the percent of superficial cells:

Treatment Group	Week 2	Week 4	Week 8	Week 12 (LOCF)
10 mcg estradiol vaginal tablet	24 (44.51)	16.6 (18.27)	15.8 (20.26)	13.2 (20.00)
Placebo vaginal tablet	5.4 (13.96)	5.2 (11.37)	5.0 (11.52)	3.8 (11.76)

In response to the Agency December 27, 2007 request to provide a table showing the mean change from baseline in the percentage of superficial and parabasal cells for the 10 mcg Vagifem and placebo treatment groups for subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom (the reviewer refers to this population as mITT-1), the Applicant reported the following as the "Revised ITT population based on the FDA criteria".

Table 9: Number of Subjects Included in the "Revised ITT Population Based on FDA Criteria"

Treatment	**Original Number of Subjects in ITT**	**Number of Subjects Excluded Based on FDA Criteria**	**Revised ITT (Original ITT minus Excluded Subjects**
10 mcg estradiol vaginal tablet	204	53	151
Placebo vaginal tablet	102	25	77
Total	306	78	228

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated January 25, 2008, Table 3, page 7 of 15.

Note from applicant: "While most bothersome symptom and vaginal cytology superficial/parabasal cells parameters were evaluated at baseline, vaginal pH parameters from screening were used. Vaginal pH at baseline was assessed as less than or greater than pH = 5 at baseline; therefore, data from screening where individual vaginal pH was actually measured was used in the analysis."

The Applicant submitted the following information for the percentages of parabasal and superficial cells incorporating the numbers for the "Revised ITT population based on the FDA criteria".

Table 10: Analysis of Vaginal Maturation Index – "Revised ITT Population Based on FDA Criteria"

	Observed Data		**Change from Baseline**	
Parabasal Cells (%)				
Visit Treatment	N	Mean (SD)	N	Mean (SD)
Baseline				
10 mcg estradiol vaginal tablet	151	47.4 (41.84)	-	-
Placebo vaginal tablet	77	49.4 (41.81)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	148	5.6 (18.37)	148	-42.5 (45.67)
Placebo vaginal Tablet	77	39.7 (36.11)	77	-10.2 (44.33)
P-value				<0.001
Superficial Cells (%)				
Visit Treatment	N	Mean (SD)	N	Mean (SD)
Baseline				
10 mcg estradiol vaginal tablet	151	0.6 (1.55)	-	-
Placebo vaginal Tablet	77	0.2 (0.61)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	148	15.3 (16.56)	148	14.7 (16.67)
Placebo vaginal Tablet	77	4.8 (8.05)	77	4.7 (8.04)
P-value	-	-	-	<0.001

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated January 25, 2008, Table 4 and Table 6, page 8 of 15.

Corrected information provided by the Applicant on April 17, 2008 showed the following:

Table 11: Number of Subjects Included in the "Revised ITT Population Based on FDA Criteria"

Treatment	**Original Number of Subjects in ITT**	**Number of Subjects Excluded Based on FDA Criteria**	**Revised ITT (Original ITT minus Excluded Subjects**
10 mcg estradiol vaginal tablet	204	55	149
Placebo vaginal tablet	102	25	77
Total	306	80	226

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated April 17, 2008, Table 3, page 7 of 15.
Note from Applicant: "While most bothersome symptom and vaginal cytology superficial/parabasal cells parameters were evaluated at baseline, vaginal pH parameters from screening were used. Vaginal pH at baseline was assessed as less than or greater than pH = 5 at baseline; therefore, data from screening where individual vaginal pH was actually measured was used in the analysis."

Medical Officer's Comments:

On April 17, 2008, the Applicant submitted a correction to their January 25, 2008 response to the Agency's requested information. As shown in Table 11, this revised information reflects a change in the total subject numbers meeting the Agency's recommended inclusion criteria (pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom) from 228 to 226. The "Revised ITT population based on FDA criteria" for the 10 mcg estradiol vaginal tablet treatment group was reduced by 2 from 151 to 149. Per the April 17, 2008 amendment, "This change in subject numbers had no effect on the results."

The corrected subject numbers and reported findings are shown in the following table.

Table 12: Analysis of Vaginal Maturation Index – "Revised ITT Population Based on FDA Criteria" (April 17, 2008)

	Observed Data		**Change from Baseline**	
Parabasal Cells (%)				
Visit Treatment	N	Mean (SD)	N	Mean (SD)
Baseline				
10 mcg estradiol vaginal tablet	149	47.8 (41.92)	-	-
Placebo vaginal tablet	77	49.8 (41.81)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	146	5.7 (18.48)	146	-42.5 (45.84)
Placebo vaginal Tablet	77	39.7 (36.11)	77	-10.2 (44.33)
P-value				<0.001
Superficial Cells (%)				
Visit Treatment	N	Mean (SD)	N	Mean (SD)
Baseline				

10 mcg estradiol vaginal tablet	149	0.5 (1.21)	-	-
Placebo vaginal Tablet	77	0.2 (0.61)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	148	15.3 (16.64)	146	14.7 (16.76)
Placebo vaginal Tablet	77	4.8 (8.05)	77	4.7 (8.04)
P-value	-	-	-	<0.001

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated April 17, 2008, Table 4 and Table 6, page 8 of 15.

Medical Officer's Comments:

Based on the Applicant's April 17, 2008 reported mean change in the proportion of superficial and parabasal cells between baseline and week 12, treatment with 10 mcg estradiol vaginal tablet statistically increased the mean percentage of superficial cells from baseline to week 12 ($p< 0.001$) and statistically decreased the mean percentage of parabasal cells from baseline to week 12 ($p< 0.001$) compared to the placebo vaginal tablet in the "Revised ITT population based on FDA criteria" who, at baseline, met the following three inclusion criteria: vaginal pH > 5, superficial cells ≤ 5% and self-identification of a moderate to severe symptom identified as most bothersome.

Vaginal pH:

See page 32 of this review for a completed discussion of vaginal pH pertaining to sNDA 20-908/SE2-013.

Per the Final Clinical Trial Report for Study VAG-2195, "--- subjects were required to have vaginal pH > 5.0. Since pH values occur anywhere on a continuum the pH values were grouped (< 5.0, 5-5.49, 5.5-6.49, > 6.49) for more meaningful comparisons. The clinical significance of the grouping was that pH < 5.0 would be indicative of a lack of vaginal endometrial atrophy, pH of 5-5.49 would indicate mild vaginal atrophy, pH 5.5-6.49 would indicate moderate vaginal atrophy, and a pH ≥ 6.49 would indicate severe atrophy." "Additionally, the categories of vaginal pH were graded on a 4 point scale (pH < 5 = 0, pH 5-5.49 = 1, pH 5.5-6.49 = 2, pH > 6.49 = 3)."

The following information on vaginal pH was included in the original sNDA 20-908/SE2-013 submission.

Table 13: Vaginal pH

Visit	Vaginal pH	Grade[a]	10 mcg Estradiol Vaginal Tablet n (%)	Placebo Vaginal Tablet N (%)
Baseline	< 5	0	3 (1.5)	0
	5 – 5.49	1	26 (12.7)	9 (8.8)
	5.5 – 6.49	2	90 (44.1)	46 (45.1)
	> 6.49	3	85 (41.7)	47 (46.1)
Week 12 (LOCF)	< 5	0	63 (31.2)	7 (6.9)
	5 – 5.49	1	82 (40.6)	30 (29.4)
	5.5 – 6.49	2	49 (24.3)	28 (27.5)
	> 6.49	3	8 (4.0)	37 (36.3)

Source: sNDA 20-908/SE2-013, Final Clinical Study Report, Table 11-4, page 67 of 1407.
a. Grade 0 = no atrophy; 1 = mild atrophy; 2 = moderate atrophy, 3 = severe atrophy.

Based on the information presented in Table 13, the Applicant stated: "At baseline the majority of subjects in both treatment groups (placebo: 91.2%, Vagifem 10 µg: 85.8%) had vaginal pH ≥ 5.5. Over 40% of subjects in both treatment groups had vaginal pH > 6.5. After 12 weeks of treatment, there was a clear shift in the numbers of subjects towards more acidic vaginal pH. In the Vagifem 10 µg-treated group 71.8% had pH < 5.5 compared to 36.3% in the placebo treatment group."

Medical Officer's Comments:

Focusing on the numbers of subjects with a vaginal pH of < 5 at week 12 (not 5.5 as utilized by the Applicant), Table 13 shows that 31.2% (63 of 202 subjects) in the 10 mcg estradiol vaginal tablet treatment group versus 6.9% (7 of 102 subjects in the placebo vaginal tablet treatment group) had a vaginal pH < 5 at week 12. However, this data does not represent the population who, at baseline, met the following three inclusion criteria: vaginal pH > 5, superficial cells ≤ 5% and self-identification of a moderate to severe symptom identified as most bothersome.

In response to the Agency December 27, 2007 request to provide this information, the Applicant submitted the following information on January 25, 2008.

Table 14: Analysis of Vaginal pH – "Revised ITT Population Based on FDA Criteria"

	Observed Data		Change from Baseline	
Visit Treatment	N	Mean (SD)	N	Mean (SD)
Baseline				
10 mcg estradiol vaginal tablet	151	2.3 (0.67)	-	-
Placebo vaginal tablet	77	2.4 (0.64)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	149	1.0 (0.87)	149	-1.3 (1.02)
Placebo vaginal Tablet	77	2.0 (0.99)	77	-0.4 (0.77)

P-value				<0.001

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated January 25, 2008, Table 8, page 9 of 15.

On April 17, 2008, the Applicant submitted a correction to their January 25, 2008 response to the Agency's requested information.

Table 15: Analysis of Vaginal pH – "Revised ITT Population Based on FDA Criteria"

	Observed Data		Change from Baseline	
Visit Treatment	N	Mean (SD)	N	Mean (SD)
Baseline				
10 mcg estradiol vaginal tablet	149	2.3 (0.67)	-	-
Placebo vaginal tablet	77	2.4 (0.64)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	147	1.0 (0.87)	147	-1.3 (1.02)
Placebo vaginal Tablet	77	2.0 (0.99)	77	-0.4 (0.77)
P-value				<0.001

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated April 17, 2008, Table 8, page 9 of 15.

Medical Officer's Comments:

For Phase 3a Study VAG-2195, the Applicant utilized a pH test strip to measure vaginal pH. To select subjects with a vaginal pH > 5.0 (one of the recommended inclusion criteria), the observed reading of the vaginal pH test strip were recorded within four intervals, as a score (not a calculated value), corresponding to pH < 5.0 – 0 (no atrophy), pH 5-5.49 = 1 (mild atrophy), pH 5.5-6.49 = 2 (moderate atrophy), or pH > 6.49 = 3 (severe atrophy) as stated in the study protocol. Therefore, the case report form for each individual subject captured the observed vaginal pH in the four stated intervals as a pH score and not as a pH value at baseline and week 12.

From the information presented in Table 15 above, a baseline mean pH score of 2.3 for the 10 mcg estradiol vaginal tablet treatment group and a baseline mean score of 2.4 for the placebo vaginal tablet treatment group demonstrates that baseline vaginal pH in the study population exceeded a pH of 5.5. The mean change in the vaginal pH score at week 12 (-1.3 in the 10 mcg estradiol vaginal tablet treatment group versus -0.4 in the placebo vaginal tablet treatment group) demonstrated a statistically significant difference between baseline and week 12 (p< 0.001).

Based on the Applicant's April 17, 2008 reported mean change in vaginal pH between baseline and week 12, (Table 15) treatment with 10 mcg estradiol vaginal tablet demonstrated a statistically significant reduction in vaginal pH between baseline and week 12 compared to the placebo vaginal tablet in the "Revised ITT population based on FDA criteria" who, at baseline, met the following three inclusion criteria: vaginal pH > 5, superficial cells ≤ 5% and self-identification of a moderate to severe symptom identified as most bothersome (p< 0.001).

The reviewer concurs with the use of a vaginal pH score in this submission. A pH score is consistent with labeling for the approved Vagifem® 25 mcg drug product.

Most Bothersome Vulvar and Vaginal Atrophy Symptom:

Per the Final Clinical Trial Report for Study VAG-2195 included in the submission, vaginal dryness and dyspareunia were the most commonly reported moderate to severe and most bothersome symptoms at baseline. See Table 16.

Table 16: Frequency of Most Bothersome Symptoms at Baseline

			Severity of Symptoms			
Symptoms	**Vaginal Tablet Treatment**	**N/A n (%)**	**None n (%)**	**Mild n (%)**	**Moderate n (%)**	**Severe n (%)**
Dryness	10 mcg E2	-	0	5 (2.5)	41 (20.1)	12 (5.9)
	Placebo	-	0	2 (2.0)	24 (23.5)	1 (1.0)
Irritation	10 mcg E2	-	0	2 (1.0)	15 (7.4)	8 (3.9)
	Placebo	-	0	3 (2.9)	6 (5.9)	1 (1.0)
Soreness	10 mcg E2	-	0	0	3 (1.5)	2 (1.0)
	Placebo	-	0	0	0	0
Dysuria	10 mcg E2	-	0	2 (1.0)	0	1 (0.5)
	Placebo	-	0	0	0	0
Dyspareunia	10 mcg E2	2 (1.0)	0	5 (2.5)	37 (18.1)	63 (30.9)
	Placebo	1 (1.0)	0	4 (3.9)	20 (19.6)	37 (36.3)
Bleeding with sexual activity	10 mcg E2	0	0	1 (0.5)	1 (0.5)	1 (0.5)
	Placebo	0	0	0	0	0

Source: Adapted from sNDA 20-908/SE2-013, Final Clinical Trial Report, Table 11-5, page 59 of 1507.
E2 = Estradiol

In Phase 3a Study VAG-2195, the severities of symptoms were graded on a 4-point scale as follows: none = 0, mild = 1, moderate = 2, and severe = 3.

Medical Officer's Comments:

Table 16 shows that 100 subjects (49.7%) in the 10 mcg estradiol vaginal tablet treatment group and 57 subjects (55.9%) in the placebo vaginal tablet treatment group selected dyspareunia as moderate to severe and most bothersome. Dryness was selected by the next largest percentage of subjects: 53 subjects (26.4%) in the 10 mcg estradiol vaginal tablet treatment group and 25 subjects (24.5%) in the placebo vaginal tablet treatment group. Irritation was selected by fewer subjects (23 subjects [11.4%] in the 10 mcg estradiol vaginal tablet treatment group and 7

subjects [3.5] in the placebo vaginal tablet treatment group). The remaining symptoms of soreness, dysuria, and bleeding with sexual activity were either not selected or selected by only a few subjects. The distribution of symptoms selected as moderate to severe and most bothersome in Study VAG-2195 is the same as observed in other clinical trials conducted in support of a VVA indication.

In the submission, the Applicant presented data demonstrating the mean change from baseline for both treatment groups (active and placebo). This data is presented in the following table.

Table 17: Mean Score and Change in Mean Score of Most Bothersome Symptoms

Symptom	**Vaginal Tablet Treatment**	**Baseline**		**Week 12 (LOCF)**		**Change from Baseline**
		n	**Mean (SD)**	**n**	**Mean (SD)**	**Mean (SD)**
Dryness	10 mcg E2	58	1.12 (0.53)	27	0.90 (0.74)	-1.22 (0.94)
	Placebo	27	1.96 (0.34)	58	1.11 (0.80)	-0.85 (0.82)
Irritation	10 mcg E2	25	2.24 (0.60)	25	1.04 (0.73)	-1.20 (0.87)
	Placebo	10	1.80 (0.63)	10	1.00 (0.67)	-0.80 (0.92)
Soreness	10 mcg E2	5	2.40 (0.55)	5	0.80 (1.30)	-1.60 (1.67)
	Placebo	0	-	0	-	-
Dysuria	10 mcg E2	3	1.67 (1.15)	3	1.00 (1.00)	-0.67 (0.58)
	Placebo	0	-	0	-	-
Dyspareunia	10 mcg E2	105	2.55 (0.59)	83	1.29 (0.93)	-1.22 (0.87)
	Placebo	61	2.54 (0.62)	49	1.65 (0.93)	-0.90 (0.98)
Bleeding with sexual activity	10 mcg E2	3	2.00 (1.00)	3	0.33 (0.58)	-1.67 (0.58)
	Placebo	0	-	0	-	-

Source: Adapted from sNDA 20-908/SE2-013, Final Clinical Trial Report, Table 11-6, page 60 of 1507.
E2 = Estradiol

Medical officer's Comments:

In Table 17, the mean baseline severity scores for the symptom dyspareunia were comparable for the 10 mcg estradiol and placebo vaginal tablet treatment groups (2.55 versus 2.54, respectively). This was not the case for the other vaginal symptoms assessed. The mean baseline scores for the symptom dryness were below 2 (score of 2 represents moderate severity) for both treatment groups indicating the inclusion of subject who scored dryness as mild.

Table 17 also demonstrates a decrease between baseline and week 12 in the number of subject who identified dyspareunia as their most bothersome symptom (105 down to 83 subjects in the 10 mcg estradiol vaginal tablet treatment group and 61 down to 49 in the placebo vaginal tablet treatment group). Per the submission, this decrease "can be explained by the fact that at Week 12 (LOCF) more subjects selected N/A (i.e., due to not having been sexually active since the last visit and therefore not having had symptoms of dyspareunia) as their response instead of mild, moderate or severe."

However, the data presented in Table 17 does not meet the Agency's recommended analysis for demonstrating product effectiveness for the third co-primary endpoint – mean change from

baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. Table 17 includes subjects who, at baseline, identified the symptom as mild and most bothersome. In addition, Table 17 does not represent the study population who, at baseline, met the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom.

On December 27, 2007, the Agency requested the Applicant to provide the following information: "For subjects meeting the enrollment criteria of pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, provide a table showing the mean change from baseline in the most bothersome moderate to severe vulvar and vaginal atrophy symptom for each symptom included in the subject self-assessment questionnaire (dryness, irritation, soreness, dysuria, dyspareunia, and bleeding with sexual activity). Include only those subjects who scored the individual symptom as moderate to severe (not mild) and identified the symptom as most bothersome at baseline."

The following table shows the revised information provided by the Applicant on January 25, 2008.

Table 18: Analysis of the Composite Most Bothersome Vulvar and Vaginal Atrophy Symptoms Over Time – "Revised ITT Population Based on FDA Criteria"

	Observed Data		**Change from Baseline**	
Visit Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Baseline				
10 mcg estradiol vaginal tablet	151	2.45 (0.50)	-	-
Placebo vaginal tablet	77	2.43 (0.50)	-	-
Week 12 (LOCF)				
10 mcg estradiol vaginal tablet	133	1.06 (0.87)	133	-1.36 (0.87)
Placebo vaginal Tablet	68	1.47 (0.92)	68	-0.94 (0.88)
P-value				<0.001

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated January 25, 2008, Table 10, page 11 of 15.

Medical Officer's Comments:

Table 18 is a composite of all subjects who identified any self-assessed symptom as moderate to severe symptom and indicated that the symptom was most bothersome to her. Table 18 provides a combined mean change from baseline to week 12 in all most bothersome moderate to severe vulvar and vaginal atrophy symptoms. Table 18 does not, however, provide information for the mean change from baseline for each individual symptom, and does not meet the recommendation

of the Agency's 2003 draft clinical evaluation guidance for the moderate to severe self-assessed vaginal symptom identified as the most bothersome co-primary endpoint:

- *Mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her. The primary analysis should show statistically significant improvement in the moderate to severe symptom identified by the subject as most bothersome to her.*

The reviewer was able to extract information for each symptom from data that was included in the January 25, 2008 submission, however. This data is shown in Table 19.

Table 19: Analysis of Most Bothersome Moderate to Severe Vulvar and Vaginal Atrophy Symptom – "Revised ITT Population Based on FDA Criteria" (LOCF)

Symptom	**Vaginal Tablet Treatment**	**Baseline Observed Data**		**Week 12 (LOCF) Observed Data**		**Change from Baseline P-value**
		n	**Mean (SD)**	**n**	**Mean (SD)**	**Mean (SD)**
Dryness	10 mcg E2 Placebo	38 22	2.13 (0.34) 2.05 (0.21)	38 22	0.74 (0.69) 1.14 (0.83)	-1.39 (0.82) -0.91 (0.81) **p=0.061**
Irritation	10 mcg E2 Placebo	22 6	2.32 (0.48) 2.17 (0.41)	22 6	1.05 (0.72) 1.17 (0.75)	-1.27 (0.88) -1.00 (0.89) **p=0.756**
Soreness	10 mcg E2 Placebo	4 0	2.50 (0.58) -	4 0	0.25 (0.50) -	-2.25 (0.96) -
Dysuria	10 mcg E2 Placebo	1 0	3.00 (-) -	1 0	2.00 (-) -	-1.00 (-) -
Dyspareunia	10 mcg E2 Placebo	84 49	2.62 (0.49) 2.63 (0.49)	66 40	1.30 (0.94) 1.70 (0.94)	-1.30 (0.89) -0.95 (0.93) **p=0.042**
Bleeding with sexual activity	10 mcg E2 Placebo	2 0	2.50 (0.71) -	2 0	0.50 (0.71) -	-2.00 (0.00) -

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated January 25, 2008, Table 99.5.2.
E2 = Estradiol.

On April 17, 2008, the Applicant submitted a correction to their January 25, 2008 response to the Agency's requested information. The following table represents the corrected data for each individual moderate to severe vulvar and vaginal atrophy symptom identified as most bothersome.

Table 20: Analysis of Most Bothersome Moderate to Severe Vulvar and Vaginal Atrophy Symptom – "Revised ITT Population Based on FDA Criteria" (LOCF)

Symptom	**Vaginal Tablet Treatment**	**Baseline Observed Data**	**Week 12 (LOCF) Observed Data**	**Change from Baseline P-value**

		n	Mean (SD)	n	Mean (SD)	Mean (SD)
Dryness	10 mcg E2 Placebo	37 22	2.14 (0.35) 2.05 (0.21)	37 22	0.76 (0.68) 1.14 (0.83)	-1.38 (0.83) -0.91 (0.81) **p=0.079**
Irritation	10 mcg E2 Placebo	22 6	2.32 (0.48) 2.17 (0.41)	22 6	1.05 (0.72) 1.17 (0.75)	-1.27 (0.88) -1.00 (0.89) **p=0.756**
Soreness	10 mcg E2 Placebo	3 0	2.33 (0.58) -	3 0	0.33 (0.50) -	-2.00 (1.00) -
Dysuria	10 mcg E2 Placebo	1 0	3.00 (-) -	1 0	2.00 (-) -	-1.00 (-) -
Dyspareunia	10 mcg E2 Placebo	84 49	2.62 (0.49) 2.63 (0.49)	66 40	1.30 (0.94) 1.70 (0.94)	-1.30 (0.89) -0.95 (0.93) **p=0.042**
Bleeding with sexual activity	10 mcg E2 Placebo	2 0	2.50 (0.71) -	2 0	0.50 (0.71) -	-2.00 (0.00) -

Source: Adapted from sNDA 20-908/SE2-013 Response to Request for Information dated April 17, 2008, Table 99.5.2.
E2 = Estradiol

Medical Officer's Comments:

Table 20 demonstrates data received from the Applicant on April 17, 2008 that represents those subjects who at baseline had a vaginal pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom. The analyses presented in Table 20 for Study VAG-2195 are based on an Analysis of Covariance (ANCOVA) for the between group comparison with treatment as a fixed effect and corresponding baseline value as a covariate without the normality assumption. Per the Applicant, "With a sample size of this magnitude, the robustness of the ANCOVA model can reasonably be assured by the central limit theory, without the normality assumption."

As shown in Table 20, analyses were performed on change from baseline scores for the individual symptoms of dryness, irritation, soreness, dysuria, dyspareunia, and bleeding with sexual activity at week 12 (with LOCF). P-values are presented for the symptom of vaginal dryness, vaginal irritation, and dyspareunia. The vaginal symptoms of soreness, dysuria, and bleeding with sexual activity had too few subjects to produce a statistically meaningful result.

Table 20 demonstrates that dyspareunia is the only symptom with a statistically significant difference between baseline and week 12 for the 10 mcg estradiol vaginal tablet compared to the placebo vaginal tablet (p=0.042).

However, the Statistical Reviewer determined that the Applicant did not adjust for multiple comparisons in the analyses submitted.

On July 31, 2008, the Applicant was notified of the following:

"Our review of supplemental NDA 20-908/SE2-013 is ongoing. At this time, we have confirmed the following p-values as provided in your April 17, 2008 submission: p = 0.079 for vaginal dryness, p = 0.756 for vaginal irritation and p = 0.042 for dyspareunia. These p-values are subject to adjustment for multiplicity. For any one of the three comparisons to be considered statistically significant, the p-value has to be less than 0.016 with a Bonferroni adjustment." The observed p-values for vaginal dryness, vaginal irritation, and dyspareunia are all greater than 0.016."

The Applicant responded on August 20, 2008 indicating that "The statistical methods section of the protocol for VAG-2195 did not indicate a plan for evaluating "individual" most bothersome symptoms nor did the Division request statistical calculations to account for an "individual symptom" during the protocol review."; "Adjustment for multiplicity was not part of the statistical analyses --."; "-- the Division's adjustment for multiplicity (Bonferroni adjustment) is not applicable." "-- a hierarchical testing procedure based on the rank order of the symptoms" "would be clinically meaningful and appropriate."

Per the Statistical Reviewer, however, additional analyses showed that the use of ANCOVA was not valid. Therefore, the Statistical Reviewer performed analyses for the individual most bothersome moderate to severe symptoms of vaginal dryness, vaginal irritation, and dyspareunia using an ANCOVA on ranks because the normality assumption for using an ANCOVA was not met. Table 21 shows these results. The mITT-1 population in Table 21 represents a subset of subjects that includes those subjects who at baseline had a vaginal pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom. The mITT-2 population in Table 21 represents all subjects who at baseline had a self-identified moderate to severe most bothersome symptom (without regard to vaginal pH or the percentage of vaginal superficial cells on a vaginal smear).

Table 21: Mean Change from Baseline to Week 12 for Estradiol Vaginal Tablet and Placebo Treated Subjects Who Reported a Moderate to Severe Most Bothersome Symptom at Baseline (Study VAG-2195 – LOCF Analysis)

Parameter	Population Analyzed	Estradiol Vaginal Tablet 10 mcg		Placebo Vaginal Tablet		P-value
		n	Mean	n	Mean	
Dyspareunia	mITT-1	73	-1.29	42	-0.93	0.0557
	mITT-2	85	-1.22	48	-1.00	0.2018
Dryness	mITT-1	33	-1.45	18	-1.11	0.3073
	mITT-2	47	-1.40	21	-1.10	0.5518
Irritation	mITT-1	20	-1.35	6	-1.00	0.6378
	mITT-2	21	-1.33	7	-1.14	0.8853

mITT-1: Subjects meeting all 3 criteria for vulvar and vaginal atrophy (i.e., moderate to severe most bothersome symptom, vaginal pH > 5.0, and vaginal superficial cells ≤ 5%).
mITT-2: Subjects meeting criteria of moderate to severe most bothersome symptom without regard to vaginal pH or percentage of vaginal superficial cells.

Medical Officer's Comments:

On September 22, 2008, the Applicant was provided the following comments regarding their August 20, 2008 submission: "—we continue to believe that (1) the primary analysis for the most bothersome symptom co-primary endpoint in your NDA be based on the individual symptoms of pain associated with intercourse, vaginal dryness, and vaginal irritation and (2) the analysis be subject to an adjustment for multiple comparisons. A hierarchal testing procedure is not an appropriate adjustment because the specifics of the procedure were not prespecified in the protocol."

The September 22, 2008 communication with the Applicant also provided the Agency's findings as presented in Table 21 indicating that a statistical adjustment for multiple comparisons is not necessary because no p-values were less than 0.05.

See the Agency's letter dated September 22, 2008 for the complete response to the Applicant's August 20, 2008 submission.

In a teleconference on September 24, 2008, the Agency requested the Applicant's comments on a subject list for the dyspareunia symptom from Study VAG-2195. The Applicant responded on September 26, 2008, and provided the following analysis for dyspareunia based on the subject list created by the Agency.

Table 22: "Analysis of Most Bothersome Urogenital Symptoms Over Time – MITT Population Pain with Intercourse"

Symptom	**Vaginal Tablet Treatment**	**Baseline Observed Data**		**Week 12 (LOCF) Observed Data**		**Change from Baseline P-value**
		n	**Mean (SD)**	**n**	**Mean (SD)**	**Mean (SD)**
Dyspareunia	10 mcg E2	84	2.6 (0.49)	76	1.4 (0.99)	-1.3 (0.91)
	Placebo	49	2.6 (0.49)	46	1.8 (0.92)	-0.8 (0.92)
						p=0.015

Source: Adapted from sNDA 20-908/SE2-013 submissions dated September 26, 2008.
E2 = Estradiol

Medical Officer's Comments:

The data submitted by the Applicant as demonstrated in Table 22 is based on an ANCOVA analysis which does not meet the normality assumption. The Applicant was requested to provide an ANCOVA on rank analysis after testing for normality.

The following additional information was provided by the Applicant on September 30, 2008 and October 1, 2008.

Table 23: "Analysis of Most Bothersome Urogenital Symptoms Over Time – MITT Population Pain with Intercourse – ANCOVA on the Rank"

Symptom	Vaginal Tablet Treatment	Baseline Observed Data		Week 12 (LOCF) Observed Data		Change from Baseline P-value
		n	Mean (SD)	n	Mean (SD)	Mean (SD)
Dyspareunia	10 mcg E2	84	2.6 (0.49)	76	1.4 (0.99)	-1.3 (0.91)
	Placebo	49	2.6 (0.49)	46	1.8 (0.92)	-0.8 (0.92)
						p=0.017

Source: Adapted from sNDA 20-908/SE2-013 submissions dated September 30, 2008 and October 1, 2008.
E2 = Estradiol

Medical Officer's Comments:

The Agency and the Applicant communicated several additional times regarding the number of subjects to be included in the mITT-1 population analysis (subjects who reported a moderate to severe and most bothersome symptom at baseline who also had a vaginal pH > 5.0, and vaginal superficial cells ≤ 5%) . Table 24 shows the agreed upon mITT-1 population.

Table24: Distribution of Subjects who Reported Symptoms as Most Bothersome at Baseline

	10 mcg Estradiol Vaginal Table		*Placebo Vaginal Tablet*	
Symptoms	***n***	***Mean***	***n***	***Mean***
Vaginal Dryness	*36*	*2.14*	*22*	*2.05*
Irritation/Itching	*21*	*2.32*	*6*	*2.17*
Dyspareunia	*76*	*2.62*	*46*	*2.63*

Source: Adapted from the Statistical Review of sNDA 20-908/SE2-013 dated October 6, 2008.

Using the agreed upon mITT-1 population and an analysis using rank ANCOVA, the Statistical Reviewer presented the following findings in the Statistical Review dated October 6, 2008. The mITT-1 population in Table 25 represents a subset of subjects that includes those subjects who at baseline had a vaginal pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom. The mITT-2 population in Table 25 represents all subjects who at baseline had a self-identified moderate to severe most bothersome symptom (without regard to vaginal pH or the percentage of vaginal superficial cells on a vaginal smear). See Table 25.

Table 25: Mean Change from Baseline to Week 12 for Estradiol Vaginal Tablet and Placebo Treated Subjects Who Reported a Moderate to Severe Most Bothersome Symptom at Baseline (Study VAG-2195 – LOCF Analysis)

Parameter	Population Analyzed	Estradiol Vaginal Tablet 10 mcg		Placebo Vaginal Tablet		P-value*
		n	Mean	n	Mean	
Dyspareunia	mITT-1	76	-1.26	46	-0.89	0.0200
	mITT-2	89	-1.21	52	-1.96	0.1164
Dryness	mITT-1	36	-1.35	25	-0.92	0.0929
	mITT-2	52	-1.40	21	-1.10	0.2207
Irritation	mITT-1	21	-1.33	6	-1.00	0.7140
	mITT-2	22	-1.32	7	-1.14	0.8352

Source: Adapted from the Statistical Review dated October 6, 2008, Table 4 on page 7 and Table 5 on page 9
* From ANCOVA on ranks with treatment effect and baseline values as a covariate included in the model.

Definitions:
mITT-1: Subjects meeting all 3 criteria for vulvar and vaginal atrophy (i.e., moderate to severe most bothersome symptom, vaginal pH > 5.0, and vaginal superficial cells ≤ 5%).
mITT-2: Subjects meeting criteria of moderate to severe most bothersome symptom without regard to vaginal pH or percentage of vaginal superficial cells.

Medical Officer's Review:

After adjusting for multiplicity, the reported findings for the symptom of dyspareunia for the mITT-1 population (p=0.0200) does not demonstrate a statistically significant improvement for the 10 mcg estradiol vaginal tablet as compared with the placebo vaginal tablet. A statistical adjustment for multiple comparisons is not necessary for the symptoms of vaginal dryness and vaginal irritation/itching because these p-values were not less than 0.05.

6.1.5 Clinical Microbiology

Per the Chemistry, Manufacturing and Controls review, Study VAG-2195 used drug product manufactured with the approved chemistry, manufacturing and controls. No clinical microbiology consult is needed for sNDA 20-908/SE2-013.

6.1.6 Efficacy Conclusions

The results from the analyses for the first 12 weeks of double-blind Phase 3a Study VAG-2195, for the subset of subjects who at baseline had a vaginal pH greater than 5, less than or equal to 5% superficial cells on a vaginal smear, and a self-identified moderate to severe most bothersome symptom, do not demonstrate effectiveness for the 10 mcg estradiol vaginal tablet versus the placebo vaginal tablet for the "(b)(4)" Per the Agency's 2003 draft clinical evaluation guidance document, the mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her is one of three recommended co-primary endpoints. When adjusted for multiplicity, Phase 3a Study VAG-2195 results do not demonstrate a statistically significant difference versus placebo for any of the following vaginal symptoms: dryness, irritation, soreness, dysuria, pain associated with sexual activity, or bleeding associated with sexual activity. A statistically significant difference versus placebo for the 10 mcg estradiol vaginal tablet for the remaining two recommended co-primary endpoints: 1) mean change from baseline to week 12 in the vaginal Maturation Index (proportion of superficial and parabasal cells) ($p < 0.001$), and 2) mean change from baseline to week 12 in vaginal pH ($p < 0.001$) was demonstrated, however.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Per the submission, the key safety endpoint in Study VAG-2195 was the "evaluation of the hyperplasia rate (determined through endometrial biopsies) at the end of study (12 months)." Endometrial biopsies were conducted both at screening (visit 1) and at the end-of-study (visit 9) using a Pipelle or another aspiration technique. All enrolled subjects were to have an evaluable biopsy at screening. Among women withdrawn from the study, only subjects treated for 3 months or longer had an end-of-treatment endometrial biopsy. The endometrial tissue obtained was processed at a central laboratory and evaluated by two independent pathologists blinded to treatment and time of study. In case of disagreement between the two pathologists, a third blinded pathologist was called upon to adjudicate the final histology determination. Assessments of endometrial biopsies were made according to predefined histologic criteria (as per the Agency's 2003 clinical evaluation guidance document). Transvaginal ultrasounds were used in addition to endometrial biopsies for the evaluation of endometrial hyperplasia.

At visit 1 (-2 to -3 weeks) and visit 9 (week 52 or end-of-study), the following additional safety evaluations were conducted: physical examination, gynecological and breast examination, cervical PAP smear (waived if smear was performed within 3 months prior to clinical trial and a normal result was reported), bilateral mammogram (not repeated at visit 1 if performed within 6 months prior to visit 1 and normal results were available), and general laboratory assessments (hematology, biochemistry, lipids, glucose metabolism parameters, and hemostasis parameters). A vaginal wet-prep for concomitant infections was performed during screening. Serum for sex hormone analysis (estradiol, estrone, estrone sulfate, sex hormone binding globulin [SHBG], follicle stimulating hormone [FSH], and luteinizing hormone [LH]) were collected at visits 1, 2, 3, 6 and 9. Vital signs were collected at each scheduled clinic visit.

The 4-Month Safety Update was submitted on April 3, 2008. Per the 4-Month Safety Update, no new or follow-up safety information, as of March 13, 2008, was available for primary, Phase 3a Study VAG-2195 or Phase 1 Study VAG-1850. Initial serious adverse event data from the ongoing non-IND European safety trial Study VAG-1748 was included in the 4-Month Safety Update.

Non-IND Study-1748 is a 52-week, open-label clinical trial being conducted in the Czech Republic, Denmark, Finland, France, Hungary, Norway, and Sweden. The primary objective of Study VAG-1748 is "to evaluate the impact of Vagifem 10 mcg tablet use on endometrial tissue in the treatment of postmenopausal vaginal atrophy". The reported preliminary safety results for Study VAG-1748 will be further discussed in Subsection 7.1.3.3, "Other significant adverse events".

7.1.1 Deaths

No deaths occurred in primary, Phase 3a Study VAG-2195 or in Phase 1 Study VAG-1850.

7.1.2 Other Serious Adverse Events

Seven (7) subjects (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [2.4%. 5 of 205 treated subjects] and 2 subjects in the placebo vaginal tablet treatment group [2%. 2 of 103 treated subjects]) in Study VAG-2195 reported serious adverse events (SAEs). The nature of these SAEs as shown below.

Study Treatment (Subject ID)	Preferred Term (AE Verbatim)
10 mcg estradiol vaginal tablet (b)(6)	Ventricular extrasystoles (premature ventricular contractions)
10 mcg estradiol vaginal tablet (b)(6)	Acute cholecystitis/cholelithiasis (acute cholecystitis/cholelithiasis)
10 mcg estradiol vaginal tablet (b)(6)	Pneumonia (pneumonia)
10 mcg estradiol vaginal tablet (b)(6)	Squamous cell carcinoma (squamous cell carcinoma, right infraorbital)
10 mcg estradiol vaginal tablet (b)(6)	Endometrial cancer, Stage II (adenocarcinoma endometrial type, Grade 2)
Placebo vaginal tablet (b)(6)	Stent occlusion (coronary artery stent closure)
Placebo vaginal tablet (b)(6)	Gastrointestinal hemorrhage (gastrointestinal hemorrhage)

No SAEs were reported in 12-week Phase 1 Study VAG-1850.

In the 4-Month Safety Update, no safety updates were made for Study VAG-1850. For Study VAG-2195, the 4-Month Safety Update indicated that "the relevant SAE safety information (e.g., preferred terms, causality, and outcomes) for Trial VAG-2195 remains the same as provided in the sNDA submission." No new SAEs were reported for Study VAG-2195 during the reporting period from July 12, 2007 to March 13, 2008.

Non-IND Study VAG-1748 was ongoing at the time of the submission of the 4-Month Safety Update. The following information was provided in the 4-Month Safety Update for this ongoing Phase 3a, 52-week, open-label study of 10 mcg estradiol vaginal tablet use in postmenopausal women with symptoms of vaginal atrophy:

- As of March 13, 2008, 335 postmenopausal women with uteri had been enrolled, 77 subjects had completed the 52-week study, 35 women had discontinued from the clinical trial, and 223 women were ongoing.

- One death had been reported in Study VAG-1748 (Subject (b)(6), 77 years of age, treatment with 10 mcg estradiol vaginal tablets from (b)(6) France). In (b)(6) was diagnosed with cerebral metastasis of a primary unknown cancer. The subject died on (b)(6) An autopsy was not performed. The event was assessed as "unlikely related" to study medication by the investigator and the Applicant.

- Eleven (11) additional subjects receiving 10 mcg estradiol vaginal tablets had SAEs. All of these additional SAEs were considered "unlikely related" to study medication by the investigator and Applicant:

  Subject (b)(6) = myocardial infarction
  Subject (b)(6) = abdominal pain
  Subject (b)(6) = melena
  Subject (b)(6) = hand fracture
  Subject (b)(6) – post-procedure hematoma
  Subject (b)(6) = wrist fracture
  Subject (b)(6) = spinal column stenosis
  Subject (b)(6) = leukemia (recurrent)
  Subject (b)(6) = meningioma
  Subject (b)(6) = colon adenoma
  Subject (b)(6) = cerebral infarction

- Subject (b)(6) and Subject (b)(6) discontinued Study VAG-1748.

- No events of endometrial hyperplasia or endometrial carcinoma have been reported in Study VAG-1748 as of the March 13, 2008 cut-off date.

Medical Officer's Comments:

In total, 7 subjects experienced serious adverse events during the conduct of 52-week Study VAG-2195 (5 subjects in the 10 mcg estradiol vaginal tablet treatment group [2.4%] and 2 subjects in the placebo vaginal tablet treatment group [2%]). Overall, the number os subjects experiencing SAEs in 52-week Study VAG-2195 is low. The 7 reported SAEs do not raise safety issues for the 10 mcg estradiol vaginal tablet.

7.1.3 Dropouts and Other Significant Adverse Events

Fifteen (15) treated subjects discontinued from Study VAG-2195 due to an adverse event, 11 (5%) in the 10 mcg estradiol vaginal tablet treatment group and 4 (4%) in the placebo vaginal tablet treatment group. One subjects randomized to the placebo vaginal tablet treatment group in Study VAG-2195 discontinued due to an adverse event prior to using any study medication. The treatment group, subject number and day to onset, and adverse event reported for the 15 treated subjects are listed below:

Subject ID (days on study to onset)	Adverse event
10 mcg estradiol vaginal tablet	
(b)(6) (onset not available)	Pneumonia
(b)(6) (day 3)	Vaginal hemorrhage, uterine spasm
(b)(6) (days 3 and 4)	Abdominal pain, back pain, vaginal discharge
(b)(6) (day 4)	Abdominal pain, back pain, pelvic discomfort
(b)(6) (day 4)	Rash
(b)(6) (day 32)	Anorexia, nausea, hot flush, depression
(b)(6) (day 45)	Vaginal discharge, vulvovaginal pruritis
(b)(6) (day 111)	Breast tenderness
(b)(6) (day 135)	Cystitis
(b)(6) (day 271)	Hepatic enzyme increased
(b)(6) (day 326)	Endometrial cancer, Stage 2
Placebo vaginal tablet	
(b)(6) (day 2)	Vaginal discharge, abdominal distention, peripheral edema, headache, back pain
(b)(6) (day 7)	Hypertension, hypoesthesia
(b)(6) (day 20)	Nausea, peripheral edema
(b)(6) (day 26)	Stent occlusion

One subject discontinued from 12-week Phase 1 Study VAG-1850. Subject 20 withdrew due to elevated liver enzymes prior to study drug administration.

Medical Officer's Comments:

As shown above, the reported adverse events resulting in discontinuation during the first 12-weeks of Study VAG-2195 (between day 1 and day 84 [week 12]) are commonly associated with estrogen therapy (for example, headache, vaginal bleeding, vaginal discharge, abdominal/pelvic pain, back pain, nausea, hot flushes, vulvovaginal pruritis, etc.). Likewise, the reported adverse events resulting in discontinuation during weeks 13 through 52 (day 85 through day 365) of unopposed estrogen use in women with uteri in Study VAG-2195 are not unexpected (for example, breast tenderness, hepatic enzyme increased, and endometrial cancer). Overall, the incidence of discontinuations due to an adverse event in 52-week Study VAG-2195 is low and does not raise safety issues.

7.1.3.1 Overall profile of dropouts

Three hundred and eight (308) subjects made up the safety population in Study VAG-2195. Fifteen (15) subjects discontinued from Study VAG-2195 due to an adverse event (4.8%, 15 of 308 treated subjects). Eleven (11) of these 15 subjects were treated with 10 mcg estradiol

vaginal tablets (5.3%, 11 of 205 treated subjects). Four (4) of these 15 subjects were treated with placebo vaginal tablets (3.8%, 4 of 103 treated subjects).

Fifty-seven (57) subjects made up the safety population in Study VAG-1850. Of the 58 subjects randomized, 1 subject discontinued prior to the administration of study medication due to elevated liver enzymes determined during screening. One other subject (Subject 12), randomized to the Vagifem® 25 mcg treatment group, was withdrawn for non-compliance with study medication on day 7. A total of 56 subjects completed treatment in Study VAG-1850.

7.1.3.2 Adverse events associated with dropouts

See Section 7.1.3 "Dropouts and Other Significant Adverse Events".

Three subjects with serious adverse events discontinued Study VAG-2195:

Subject (b)(6) = 57 years of age, 10 mcg estradiol vaginal tablet treatment group, hospitalized due to pneumonia, recovered.

Subject (b)(6) = 62 years of age, 10 mcg estradiol vaginal tablet treatment group for 324 days, endometrial biopsy diagnosis of adenocarcinoma with FIGO Grade 2 pattern (Nuclear grade = 1 and Architectural grade = 2), hospitalized for total hysterectomy and bilateral salpingo-oophorectomy with bilateral pelvic lymphadenectomy, post-surgery radiation therapy with radioactive implants to the vaginal area.

Subject (b)(6) = 55 years of age, placebo vaginal tablet treatment group for 54 days, hospitalized due to chest pain, stent replacement, recovered.

No treated subjects discontinued from Study VAG-1850 due to an adverse event.

Medical Officer's Comments:

For Subject (b)(6) and Subject (b)(6), the Applicant listed the relationship to study drug as "unlikely". For Subject (b)(6) the Applicant listed causality as "possible". Subject (b)(6) will be discussed further under Subsection 7.1.3.3 "Other significant adverse events".

7.1.3.3 Other significant adverse events

Endometrial Thickness:

All subjects in 52-week Study VAG-2195 had a transvaginal ultrasound (TVU) performed prior to an endometrial biopsy at screening and at week 52 (or sooner if clinically indicated and at

early termination). Per the study protocol, subjects whose double-wall endometrial thickness measured by TVU were > 4 mm at screening were not eligible for enrollment.

Per the submission, the mean endometrial thickness at baseline in Study VAG-2195 was 2.20 mm in the placebo-treated group and 2.31 mm in the 10 mcg estradiol-treated group. After 52 weeks of treatment, mean endometrial thickness was 2.21 in the placebo-treated group and 2.47 mm in the 10 mcg estradiol-treated group.

In 12-week Study VAG-1850, TVUs were only obtained at screening to fulfill the inclusion criteria – "Endometrial thickness < 4.0 mm (double layer), as measured by transvaginal ultrasound (if applicable)".

A total of twenty-five (25) subjects had a TVU double-wall endometrial thickness ≥ 4 mm at week 52 or at early termination in Study VAG-2195 (21 subjects in the 10 mcg estradiol vaginal tablet treatment group and 4 subjects in the placebo vaginal tablet treatment group). The following presentation demonstrates the TVU information available for these 25 subjects.

Subjects treated with 10 mcg estradiol vaginal tablet:

Subject ID	Screening TVU	End-of-Study TVU	Other Findings
(b)(6)			
	3.0 mm (day -19)	5 mm (day 367)	None
	3.5 mm (day -14)	5 mm (day 363)	None
	2 mm (day -14)	12 mm (day 322)	Posterior fibroid, possible endometrial hyperplasia
	3 mm (day -19)	5 mm (day 361)	2 small fibroids
	3 mm (day -20)	4 mm (day 375)	2 small fibroids
	2.5 mm (day -19)	12 mm (day 361)	None
	2.21 mm (day -42)	4 mm (day 362)	None
	1 mm (day -12)	4.8 mm (day 399)	2 small fibroids
	1.7 mm (day -48)	8 mm (day 380)	None
	3.2 mm (day -13)	4.1 mm (day 368)	None
	2.6 mm (day -18)	4.6 mm (day 361)	None
	1.7 mm (day -35)	6.8 mm (day 364)	None
	1.7 mm (day-119)	4.3 mm (day 365)	None
	3 mm (day -21)	7.0 mm (day 379)	None
	1 mm (day -28)	4 mm (day 360)	None
	3.11 mm (day -21)	4.66 mm (day 13)	None
	4 mm (day -39)	5.3 mm (day 369)	8 mm cyst right ovary
	3.6 mm (day -35)	5.5 mm (day 365)	None
	2 mm (day -20)	4 mm (351)	None
	2 mm (day -20)	10 mm (day 78)	None
	1 mm (day -27)	4 mm (day 289)	None

Subjects treated with placebo vaginal tablet:

Subject ID	Baseline TVU	End-of-Study TVU	Other Findings
(b)(6)	3.5 mm (day -24)	4.43 mm (day 379)	Old fibroids and calcifications noted
	2.21 mm (day -56)	5.43 mm (day 367)	None
	1.2 mm (day -23)	9 mm (day 352)	None
	3.7 mm (day -30)	6.8 mm (day 365)	None

Medical Officer's Comments:

From the reported TVU findings at week 52 (or early termination) in Study VAG-2195, 10.2% of subjects (21 of 205 treated subjects) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study TVU ≥ 4 mm compared to 3.8% of subjects (4 of 103 treated subjects) in the placebo vaginal tablet treatment group. This finding reflects the known effect of unopposed estrogen stimulation of the endometrium.

Endometrial Biopsy:

In Study VAG-2195, all subjects had a uterus and had an endometrial biopsy performed at screening and at the end-of-study or early termination provided the subjects had been treated for 3 months or longer. Subjects with endometrial hyperplasia or cancer at screening were excluded from the study. Transvaginal ultrasound (TVU) assessments were conducted preceding the endometrial biopsy. An evaluable endometrial biopsy at screening was defined as "endometrial tissue sufficient for diagnosis". Per the study protocol, if no tissue was obtained at screening the biopsy could be repeated. Endometrial biopsies with insufficient tissue for diagnosis and TVU double-wall thickness < 4 mm could be categorized as "atrophic endometrium".

Endometrial tissue obtained was "processed in the same manner by a central laboratory". Two independent pathologists blinded to treatment and time of biopsy assessed each endometrial sample. In case of disagreement between the two pathologists, a third blinded pathologist adjudicated the final histologic determination. The Agency's recommended histologic characteristics of the endometrium was followed.

One hundred and seventy-two subjects (84%, 172 of 205 treated subjects) in the 10 mcg estradiol vaginal tablet treatment group had an end-of-study endometrial biopsy performed in Study VAG-2195. Seventy-nine subjects (77%, 79 of 103 treated subjects) in the placebo vaginal tablet treatment group had end-of-study endometrial biopsies performed. The results of the screening and end-of-study endometrial biopsies are shown in Table 26.

Table 26: Endometrial Biopsy Results in Study VAG-2195

	10 mcg Estradiol Vaginal Tablet	**Placebo Vaginal Tablet**	**Total**
Subjects with endometrial biopsy, n (%)			
Screening	201 (98.0)	102 (99.0)	303 (98.4)

Week 52[a]	172 (83.9)	79 (76.7)	251 (81.5)
Histology of the endometrium, n (%)[b]			
No tissue			
Screening	19 (9.5)	10 (9.8)	29 (9.6)
Week 52	31 (18.0)	18 (22.8)	49 (19.5)
Tissue insufficient for diagnosis			
Screening	40 (19.9)	26 (25.5)	66 (21.8)
Week 52	42 (24.4)	19 (24.1)	61 (24.3)
Atrophic			
Screening	112 (55.7)	54 (52.9)	166 (54.8)
Week 52	66 (38.4)	32 (40.5)	98 (39.0)
Inactive			
Screening	23 (11.4)	9 (8.8)	32 (10.6)
Week 52	26 (15.1)	10 (12.7)	36 (14.3)
Proliferative			
Screening	0	0	0
Week 52	0	0	0
Secretory			
Screening	0	0	0
Week 52	0	0	0
Menstrual type			
Screening	0	0	0
Week 52	0	0	0
Simple hyperplasia without atypia			
Screening	0	0	0
Week 52	0	0	0
Simple hyperplasia with atypia			
Screening	0	0	0
Week 52	0	0	0
Complex hyperplasia without atypia			
Screening	0	0	0
Week 52	1 (0.5)[c]	0	1 (0.4)
Complex hyperplasia with atypia			
Screening	0	0	0
Week 52	0	0	0
Carcinoma			
Screening	0	0	0
Week 52	1 (0.6)	0	1 (0.4)
Polyps			
Screening	6 (3.0)	3 (2.9)	9 (3.0)
Week 52	3 (1.2)	0	3 (1.2)
Other			
Screening	1 (0.5)	0	1 (0.3)
Week 52	2 (1.2)	0	2 (0.8)

Source: Adapted from sNDA 20-908/SE2-013, Final Clinical Study Report, Table 12-7, page 86 of 1507.

a. All week 52 values presented are last observation carried forward (LOCF).
b. The percentages for each category of the "Histology of the endometrium" are based on the number of subjects with endometrial biopsy at screening and week 52, respectively.
c. Patient received study medication for 9 days.

Medical Officer's Comments:

In Study VAG-2195, 81.5% (251 of 308 treated subjects) had endometrial biopsies performed at end-of-study (week 52 or early termination). One hundred seventy-two (172) of these subjects were in the 10 mcg estradiol vaginal tablet treatment group and 79 subjects were in the placebo vaginal tablet treatment group). As shown in Table 26, the majority of reported outcomes include diagnoses reported as tissue insufficient for diagnoses, atrophic, inactive, proliferative, secretory, and menstrual type. These categories of endometrial biopsy outcomes resulting from unopposed estrogen stimulation of the endometrium are considered within normal histological limits. No assessment of the endometrium can be rendered, however, if the biopsy specimen contains no endometrial tissue.

In Study VAG-2195, 36% of the subjects in both treatment groups (73 of 205 treated subjects in the 10 mcg estradiol vaginal tablet treatment group and 37 of 103 treated subjects in the placebo vaginal tablet treatment group) had either no endometrial tissue present in the biopsy specimen or endometrial tissue insufficient for diagnosis. A comparison with reported end-of-study TVU results fortunately showed that the majority of these subjects had TVUs reported as < 4 mm. An endometrial biopsy result reported as endometrial tissue insufficient for diagnosis and a TVU < 4 mm is accepted to represent an endometrium without evidence of endometrial hyperplasia provided a valid attempt has been made to sample the endometrium. Such is not the case, however, for an end-of study endometrial biopsy reported as no tissue. The following subjects were reported to have end-of-study endometrial biopsies reported as no tissue or tissue insufficient for diagnosis and a TVU of 4 mm of greater:

<u>10 mcg estradiol vaginal tablet treatment group:</u>

- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 361) had a TVU reported as 12 mm (day 361)*
- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis at end-of-study (day 399) had a TVU reported as 4.8 mm (day 399)*
- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 364) had a TVU reported as 6.8 mm (day 364)*
- *Subject (b)(6)) with a diagnosis of no tissue on endometrial biopsy at end-of-study (day 365) had a TVU reported as 4.3 mm (day 365)*
- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 360) had a TVU reported as 4 mm (day 360)*

<u>Placebo vaginal tablet treatment group:</u>

- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 379) had a TVU reported as 4.43 mm (day 379)*
- *Subject (b)(6) with a diagnosis of tissue insufficient for diagnosis on endometrial biopsy at end-of-study (day 367) had a TVU reported as 5.43 mm (day 367)*

The final outcome for the 5 subjects in the 10 mcg estradiol vaginal tablet treatment group and the 2 subjects in the placebo vaginal tablet treatment group are unknown. The applicant was

requested to provide follow-up information for two subjects of particular interest: Subject (b)(6) and Subject (b)(6)

Per the follow-up information provided by the Applicant on September 3, 2008, a recording error was made on the Case Report Form for Subject (b)(6). A site monitor recorded the endometrial thickness as 12 mm. The end-of-study TVU report, obtained on (b)(6), indicated an endometrial thickness of 1.2 mm.

Follow-up information provided for Subject (b)(6) indicates that Subject (b)(6) "has received annual gynecologic care and routine medical care since the end of study visit on (b)(6) She denied any vaginal bleeding and has been offered free of charge follow-up vaginal ultrasound and/or endometrial biopsy which she refused." Therefore, no final outcome is available for Subject (b)(6).

Table 26 also demonstrates that no subjects in the placebo vaginal tablet treatment group were diagnosed with abnormal endometrial findings including polyps, endometrial hyperplasia or endometrial cancer in 52-week Study VAG-2195. The seven abnormal findings reported in Study VAG-2195 for the 10 mcg estradiol vaginal tablet treatment group are discussed below:

- Subjec (b)(6) was diagnosed with complex hyperplasia without atypia on study day 43:

  Screening double wall TVU obtained on study day -37 was reported as 3 mm
  Screening endometrial biopsy obtained on study day -37 was reported as follows:
  Pathologist 1 = Endometrium, inactive
  Pathologist 2 = Endometrium, inactive; polyp, atrophic type
  Pathologist 3 = Inactive to weak proliferation, early atrophy/weak stimulation
  Final diagnosis = Polyps

  Early termination double wall TVU obtained on study day 43 was reported as 2 mm
  Early termination endometrial biopsy obtained on study day 43 was reported as follows:
  Pathologist 1 = Inactive to weak proliferation, early atrophy/weak stimulation
  Pathologist 2 = Endometrial hyperplasia, complex type (no atypia); may be hyperplastic polyp but small sample
  Pathologist 3 = Unsatisfactory for diagnosis; limited surface endometrium present; focal area of glandular crowding without cytologic atypia
  Final diagnosis = Complex hyperplasia without atypia

Per the submission, Subject (b)(6) took study medication for a total of 9 days. Her reported symptoms prior to her termination date on day 43 included vaginal discharge (day 10), laryngeal edema (day 17), cough (day 39), and rhinorrhea (day 40).

- Subject (b)(6) was diagnosed with adenocarcinoma endometrial type, FIGO grade 2 on study day 326:

Screening double wall TVU obtained on study day -12 was reported as 2 mm; multiple small uterine fibroids
Screening endometrial biopsy obtained on study day -8 was reported as follows:
Pathologist 1 = Tissue volume too scant for diagnosis – no endometrium present
Pathologist 2 = Tissue volume too scant for diagnosis – no endometrium present
Final diagnosis = No tissue

Week 52 double wall TVU obtained on study day 322 was reported as 12 mm; homogenous endometrial thickening, possible endometrial hyperplasia
Week 52 endometrial biopsy obtained on study day 326 was reported as follows:
Pathologist 1 = Adenocarcinoma endometroid type
Pathologist 2 = Adenocarcinoma endometroid type
Final diagnosis = Carcinoma (adenocarcinoma with FIGO Grade 2 pattern; Nuclear grade = 1 and Architectural grade = 2)

Subject (b)(6) underwent a total hysterectomy and bilateral salpingo-oophorectomy along with bilateral pelvic lymphadenectomy. Cytology and surgical pathology reported adenocarcinoma endometrial type, FIGO grade 2.

- Subject (b)(6) was diagnosed with atrophic polyp on study day 359:

Screening double wall TVU obtained on study day -14 was reported as 3 mm
Screening endometrial biopsy obtained on study day -14 was reported as follows:
Pathologist 1 = Atrophic endometrial epithelium without intact glands or stroma
Pathologist 2 = Atrophic endometrial epithelium without intact glands or stroma
Final diagnosis = Atrophic

Week 52 double wall TVU obtained on study day 359 was reported as 3 mm
Week 52 endometrial biopsy obtained on study day 359 was reported as follows:
Pathologist 1 = Endometrium, atrophic (post menopausal)
Pathologist 2 = Polyp, atrophic type, inactive to weak
Pathologist 3 = Inactive to weak proliferative, early atrophy/weak stimulation
Final diagnosis = Polyps

- Subjec (b)(6) was diagnosed with atrophic polyp on study day 345:

Screening double wall TVU obtained on study day -23 was reported as 1 mm
Screening endometrial biopsy obtained on study day -23 was reported as follows:
Pathologist 1 = Atrophic endometrial epithelium without intact glands or stroma
Pathologist 2 = Atrophic endometrial epithelium without intact glands or stroma
Final diagnosis = Atrophic

Week 52 double wall TVU obtained on study day 352 was reported as 1.9 mm
Week 52 endometrial biopsy obtained on study day 345 was reported as follows:
Pathologist 1 = Endometrium, inactive

Pathologist 2 = Polyp, atrophic type
Pathologist 3 = Endometrium, inactive
Final diagnosis = Polyps

- Subject (b)(6) was diagnosed with atrophic polyp on study day 361:

  Screening double wall TVU obtained on study day -19 was reported as 3 mm, fibroids noted
  Screening endometrial biopsy obtained on study day -19 was reported as follows:
  Pathologist 1 = Atrophic endometrial epithelium without intact glands or stroma
  Pathologist 2 = Atrophic endometrial epithelium without intact glands or stroma
  Final diagnosis = Atrophic

  Week 52 double wall TVU obtained on study day 361 was reported as 5 mm; 2 fibroids noted.
  Week 52 endometrial biopsy obtained on study day 345 was reported as follows:
  Pathologist 1 = Endometrium, inactive
  Pathologist 2 = Polyp, atrophic type
  Pathologist 3 = Polyp, adenomyomatous type, mixed smooth muscle and glandular proliferation
  Final diagnosis = Polyps

- Subject (b)(6) was diagnosed with adenomyosis and atrophic polyp on study day 364:

  Screening double wall TVU obtained on study day -48 was reported as 3.8 mm
  Screening endometrial biopsy obtained on study day -48 was reported as follows:
  Pathologist 1 = Endometrium, atrophic (post menopausal)
  Pathologist 2 = Endometrium, inactive
  Final diagnosis = Atrophic

  Week 52 double wall TVU obtained on study day 364 was reported as 3.1 mm
  Week 52 endometrial biopsy obtained on study day 364 was reported as follows:
  Pathologist 1 = Adenomyosis, endometrium atrophic (post menopausal)
  Pathologist 2 = Endometrium, inactive; polyp, atrophic type
  Pathologist 3 = Endometrium, atrophic (post-menopausal); polyp, atrophic type
  Final diagnosis = Other (adenomyosis)

- Subject (b)(6) was diagnosed with atypical epithelial proliferation on study day 56:

  Screening double wall TVU obtained on study day 1 was reported as 1.7 mm
  Screening endometrial biopsy obtained on study day -21 was reported as follows:
  Pathologist 1 = Tissue volume too scant for diagnosis; no endometrium present
  Pathologist 2 = Tissue volume too scant for diagnosis; no endometrium present
  Final diagnosis = No tissue

Week 52 double wall TVU obtained on study day 56 was reported as 3.4 mm; anterior fibroids noted
Week 52 endometrial biopsy obtained on study day 364 was reported as follows:

Pathologist 1 =	Atypical epithelial proliferation (one gland had atypical architecture and eosinophilic metaplasia – likely benign metaplasia, but cannot exclude abnormality); atrophic endometrial epithelium without intact glands or stroma
Pathologist 2 =	Atrophic endometrial epithelium without intact glands or stroma
Pathologist 3 =	Tissue volume too scant for reliable diagnosis
Final diagnosis =	Other (atypical epithelial proliferation)

\
Endometrial biopsies were not performed in 12-week Study VAG-1850.

Medical Officer's Comments:

The finding of 1 case of endometrial cancer in a 52-week clinical trial of unopposed estrogen use in postmenopausal women with uteri is not unexpected. Subject (b)(6) *presented with vaginal bleeding on day 322 and was diagnosed with endometrial cancer on day 326. Estrogen class labeling advises patients and healthcare providers of the need for close clinical surveillance, including adequate measures in all cases of unusual vaginal bleeding. The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus.*

The reported baseline endometrial biopsy findings and the causality of complex hyperplasia without atypia in Subject (b)(6) *is questionable. Subject* (b)(6) *reportedly took only 9 days of study medication. No complaints of vaginal spotting/bleeding were recorded for this subject.*

The endometrial findings in Phase 3a Study VAG-2195 (1 case each of endometrial cancer and complex hyperplasia without atypia) supports the use of estrogen class labeling for the 10 mcg estradiol vaginal tablet.

Vaginal Bleeding:

In total, 12 subjects reported vaginal bleeding in Study VAG-2195 (9 in the 10 mcg estradiol vaginal tablet treatment group [4.4%, 9 of 205 treated subjects] and 3 subjects in the placebo vaginal tablet treatment group [3.0%, 3 of 103 treated subjects]). Only 1 of these 9 subjects discontinued due to the adverse event (Subject (b)(6) in the 10 mcg estradiol vaginal tablet treatment group).

Five subjects in 12-week Study VAG-1850 reported vaginal spotting (2 in the 10 mcg estradiol vaginal tablet treatment group [7%, 2 of 29 treated subjects] and 3 subjects in the Vagifem® 25 mcg treatment group [11%, 3 of 28 treated subjects]). Vaginal bleeding was not reported in Study VAG-1850.

Medical Officer's Comments:

Overall, the percentage of women reporting vaginal bleeding was low in 52-week Study VAG-2195. Similarity between the active and placebo treatment groups in the percentage of women reporting vaginal bleeding (4.4% in the 10 mcg estradiol vaginal tablet treatment group versus 3.0% in the placebo vaginal tablet treatment group) in Study VAG-2195 is noted.

In 12-week Study VAG-1850, a larger percentage of subjects reported vaginal spotting with the use of the Vagifem® 25 mcg vaginal tablet (11%, 3 of 28 subjects) than with the use of the 10 mcg estradiol vaginal tablet (7%, 2 of 29 subjects). Vaginal spotting is not an unexpected clinical outcome with estrogen therapy, however. The lower incidence of vaginal bleeding in the 10 mcg estradiol vaginal tablet treatment group may be supported by the reported reduced systemic estradiol exposure for the 10 mcg estradiol vaginal tablet as compared with 25 mcg Vagifem®. Study VAG-1850 reported an average estradiol $C_{ave\ (0.24)}$ below 20 pg/ml for all subjects at each assessment. See Section 5.1 "Pharmacokinetics" of this review for a more complete discussion of the estradiol plasma concentrations in Study VAG-1850.

7.1.4 Other Search Strategies

No algorithm involving combination of clinical findings and a marker for a particular toxicity was developed with the exception of the interrelationship between the use of unopposed estrogen in a woman with a uterus and the finding of endometrial thickness and endometrial hyperplasia/cancer as discussed in Subsection 7.1.3.3, "Other significant adverse events".

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Per the submission, safety is summarized for all randomized subjects who applied at least 1 dose of study medication. Two hundred and five (205) subjects make up the safety population of women who received the 10 mcg estradiol vaginal tablet in 52-week Study VAG-2195. Fifty-seven (57) subjects make up the safety population in 12-week Study VAG-1850.

Safety was evaluated from the results of subject reported signs and symptoms, history reported by the subject, vital sign measurements, scheduled physical examinations, and diagnostic assessments performed including mammograms, Pap smears, TVUs, and endometrial biopsies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Per the submission, all reported adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0. Pre-existing conditions found as a result of screening procedures were not reported as adverse events. Treatment-emergent adverse events

(TEAE) were defined as: 1) Events reported during the clinical trial that were not present before treatment with study medication; or 2) Events that were present prior to treatment which worsened during the clinical trial. Adverse events and TEAEs were summarized by body system and treatment group.

7.1.5.3 Incidence of common adverse events

In Phase 3a, 52-week Study VAG-2195, 235 subjects (76.3%) experienced a least one TEAE (158 of 205 treated subjects [77%] in the 10 mcg estradiol vaginal tablet treatment group and 77 of 103 treated subjects [75%] in the placebo vaginal tablet treatment group). The most commonly reported adverse events in the 10 mcg estradiol vaginal tablet treatment group were vulvovaginal mycotic infection (8.3%, 17 of 205 treated subjects), vulvovaginal pruritis (7.8%, 16 of 205 treated subjects), and headache (7.3%, 15 of 205 treated subjects). The most commonly reported adverse events in the placebo vaginal tablet treatment group were headache (12.6%, 13 of 103 treated subjects), vulvovaginal discharge (7.8%, 8 of 103 treated subjects), and nasopharyngitis (6.8%, 7 of 103 treated subjects).

In Phase 1, 12-week Study VAG-1850, 48 subjects (84.2%) experienced at least one TEAE (23 of 29 subjects [79.3%] in the 10 mcg estradiol vaginal tablet treatment group and 25 of 28 treated subjects [89.3%] in the Vagifem® 25 mcg treatment group). The most commonly reported adverse events in the 10 mcg estradiol vaginal tablet treatment group were headache (27.6%, 8 of 29 treated subjects), vaginal discharge (13.8%, 4 of 29 treated subjects), nasopharyngitis (13.8%, 4 of 29 treated subjects), and nausea (13.8%, 4 of 29 treated subjects). The most commonly reported adverse events in the Vagifem® 25 mcg treatment group were headache (32.1%, 9 of 28 treated subjects), diarrhea (17.9%, 5 of 28 treated subjects), nasopharyngitis (17.9%, 5 of 28 treated subjects), and vaginal discharge (14.3%, 4 of 28 treated subjects).

See Table 27 for more information on common adverse events in these two clinical trials. Table 27 is sorted by decreasing frequency in the 10 mcg estradiol vaginal tablet treatment group.

7.1.5.4 Common adverse event tables

Table 27: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events for ≥ 5% in Any Treatment Group

Study VAG-2195	**10 mcg Estradiol Vaginal Tablet (N=205) n (%)**	**Placebo Vaginal Tablet (N=103) n (%)**	**Total (N=308) n (%)**
Vulvovaginal mycotic infection	17 (8.3)	3 (2.9)	20 (6.5)
Vulvovaginal pruritis	16 (7.8)	2 (1.9)	18 (5.8)
Headache	15 (7.3)	13 (12.6)	28 (9.1)
Nasopharyngitis	14 (6.8)	7 (6.8)	21 (6.8)
Back pain	14 (6.8)	2 (1.9)	16 (5.2)
Vaginal discharge	12 (5.9)	8 (7.8)	20 (6.5)

Diarrhea	11 (5.4)	0 (0.0)	11 (3.6)
Study VAG-1850	**10 mcg Estradiol Vaginal Tablet (N=29) n (%)**	**Vagifem® 25 mcg (N=28) n (%)**	**Total (N=57) n (%)**
Headache	8 (27.6)	9 (32.1)	17 (29.8)
Diarrhea	3 (10.3)	5 (17.9)	8 (14.0)
Nasopharyngitis	4 (13.8)	5 (17.9)	9 (15.8)
Vaginal discharge	4 (13.8)	3 (14.3)	8 (14.0)
Nausea	4 (13.8)	1 (3.6)	5 (8.8)
Weight increase	3 (10.3)	3 (10.7)	6 (10.5)
Pharyngolaryngeal pain	3 (10.3)	1 (3.6)	4 (7.0)
Peripheral edema	3 (10.3)	1 (3.6)	4 (7.0)
Back pain	2 (6.9)	4 (14.3)	6 (10.5)
Metrorrhagia	2 (6.9)	3 (10.7)	5 (8.8)
Vomiting	2 (6.9)	2 (7.1)	4 (7.0)
Pain in extremity	2 (6.9)	1 (3.6)	3 (5.3)
Hot flush	2 (6.9)	1 (3.6)	3 (5.3)
Hematoma	2 (6.9)	-	2 (3.5)
Phlebitis	2 (6.9)	-	2 (3.5)
Flatulence	1 (3.4)	4 (14.3)	5 (8.8)
Cough	1 (3.4)	2 (7.1)	3 (5.3)
Malaise	-	2 (7.1)	2 (3.5)
Fall	-	2 (7.1)	2 (3.5)
Bronchitis	-	2 (7.1)	2 (3.5)
Dizziness	-	2 (7.1)	2 (3.5)

Source: Adapted from sNDA 20-908SE2-013, Summary of Clinical Safety Studies, Table 2-1 on page 12 of 46 and Table 2-5 on page 19 of 46.

Medical Officer's Comments:

The common reported treatment-emergent adverse events in Study VAG-2195 and Study VAG-1850 are not unknown with vaginal estrogen alone therapy. The adverse events demonstrated in Table 27 do not raise safety issues for the 10 mcg estradiol vaginal tablet product.

7.1.5.5 Identifying common and drug-related adverse events

In Study VAG-2195, a larger percentage of subjects in the 10 mcg estradiol vaginal tablet treatment group reported vulvovaginal mycotic infection/pruritis, back pain and diarrhea as compared with the placebo treatment group. Headache and vaginal discharge were reported in both treatment groups in Study VAG-2195, however, a higher incidence of these events were reported in the placebo vaginal tablet treatment group.

Overall, subjects randomized to the Vagifem® 25 mcg treatment group in Study VAG-1850 reported a higher incidence of common adverse events with the exceptions noted in Table 27.

7.1.5.6 Additional analyses and exploration

No additional analyses were performed on the reported most common treatment-emergent adverse events.

7.1.6 Less Common Adverse Events

See the discussion regarding the reported endometrial findings in Subsection 7.1.3.3 "Other significant adverse events".

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Clinical laboratory assessments of hematology (hemoglobin, hematocrit, red blood cell count [RBC], white blood cell count [WBC], platelet count), biochemistry (total bilirubin, alkaline phosphatase [AP], gamma glutamyltransferase [GGT], aspartate aminotransferase [AST], alanine aminotransferase [ALT]. Creatinine), and sex hormones (estradiol, estrone, estrone sulfate, sex hormone-binding globulin [SHBG], FSH, LH) were performed at baseline and end-of-study in Study VAG-2195.

Clinical laboratory assessments of hematology (hemoglobin, hematocrit, RBC, WBC, platelet count, mean corpuscular volume [MCV], partial thromboplastin time [a=PTT]), biochemistry (ALT, AST, GGT, total bilirubin, creatinine, potassium, glucose) and urinalysis (pH, glucose, blood, protein) were performed at the screening, baseline and end-of-study visits in Study VAG-1850. In addition, in this study, samples for the pharmacokinetic profiles for estradiol, estrone, and estrone sulfate in plasma were also obtained on days -1, 1-2, 14-15, 82-83 and 1 sample each on days 7, 30 and 58.

Medical Officer's Comments:

The laboratory assessments obtained during the conduct of the two studies in this submission appear appropriate and adequate.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

In 52-week Study VAG-2195 and 12-week Study VAG-1850, laboratory assessments were performed at screening and end-of-stud (or early termination). Clinically relevant differences, for the assessments performed, from normal reference ranges and from individual subject screening values in all treatment groups were reported in the submission.

7.1.7.3 Standard analyses and explorations of laboratory data

See the information provided in Subsection 7.1.7.1 "Overview of laboratory testing in the development program". In the submission, clinically relevant differences, for the assessments performed, from normal reference ranges and from individual subject screening values in all treatment groups were reported.

In Study VAG-2195, there were no clinically relevant differences from normal reference ranges or from screening values for any of the laboratory assessments performed for either the 10 mcg estradiol vaginal tablet treatment group or the placebo vaginal tablet treatment group. Individual subject changes were evaluated through shift tables and showed no clinically significant abnormalities.

In Study VAG-1850, similar findings are reported with one exception. Subject (b)(6) was observed to have a major laboratory deviation of clinical relevance during screening (GTT value of 290U/L). Subject (b)(6) was withdrawn from Study VAG-1850 before study drug administration.

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations of laboratory data were performed.

7.1.7.5 Special assessments

In Study VAG-2195, sex hormone levels were evaluated at baseline and weeks 2, 12, and 52. See Table 28 for the reported results.

Table 28: Mean Plasma Sex Hormone Concentrations in Study VAG-2195

Week (SD)	**Estradiol (pg/mL0**		**Estrone (pg/mL)**		**Estrone Sulfate ng/ML**	
	10 mcg E2	Placebo	10 mcg E2	Placebo	10 mcg E2	Placebo
Baseline	4.3 (10.5)	3.8 (3.1)	28 (11.7)	29 (9.5)	0.25 (.12)	0.27 (.15)
Week 2	5.2 (4.7)	3.4 (2.9)	30 (10.2)	27 (9.4)	0.31 (.17)	0.26 (.14)
Week 12	4.4 (3.9)	3.8 (2.9)	27 (10.6)	27 (8.5)	0.27 (.14)	0.27 (.13)
Week 52	3.9 (3.1)	3.6 (3.0)	29 (12.4)	27 (9.6)	0.23 (.13)	0.23 (.13)
	FSH (mIU/mL)		**LH (mIU/mL)**		**SHBG (nmol/L)**	

Baseline	88 (29.8)	89 (30.1)	40 (13.7)	42 (14.2)	56 (25.4)	54 (27.2)
Week 2	84 (26.3)	88 (29.1)	42 (13.7)	42 (14.3)	54 (23.1)	55 (28.5)
Week 12	88 (31.7)	90 (32.5)	40 (13.9)	41 (13.4)	54 (24.0)	52 (24.0)
Week 52	88 (31.6)	89 (41.1)	40 (12.9)	43 (15.9)	53 (22.6)	55 (29.6)

Source: Adapted from sNDA 20-908/SE2-013, Summary of Clinical Safety Studies, Table 3-1, page 31 of 46.
10 mcg E2 = 10 mcg estradiol vaginal tablet.

Medical Officer's Comments:

Overall, the mean plasma sex hormone levels were similar for the two treatment groups in Study VAG-2195.

Study VAG-1850 was designed to assess the systemic absorption of estradiol from the 10 mcg estradiol vaginal tablet compared to Vagifem® 25 mcg approved for the treatment of atrophic vaginitis. Differences observed in systemic estradiol exposure for the two formulations are shown in Table 29.

Table 29: Plasma Estradiol, Estrone, Estrone Sulfate Levels ($C_{ave(0-24)}$) in Study VAG-1850

Plasma Estradiol Levels ($C_{ave(0-24)}$)[a]					
Treatment	Day -1	Day 1	Day 14	Day 82[b]	Day 83[c]
10 mcg E2	3.2 (47.4)	9.4 (45.2)[d]	6.6 (57.0)[d]	1.9 (160.5)	4.6 (84.6)
Vagifem®	4.0 (51.2)	19.8 (31.3)[d]	18.3 (39.1)[d]	2.0 (208.1)[e]	9.4 (77.7)[d]
Plasma Estrone Levels ($C_{ave(0-24)}$)[a]					
10 mcg E2	15.5 (62.5)	18.6 (43.9)[d]	19.7 (32.4)[d]	15.1 (41.2)	15.9 (40.5)
Vagifem®	17.6 (39.8)	22.7 (29.9)[d]	26.9 (24.6)[d]	17.7 (43.6)	19.5 (39.7)
Plasma Estrone Sulfate Levels ($C_{ave(0-24)}$)[a]					
10 mcg E2	139.4 (59.7)	186.8 (63.5)[d]	233.3 (55.2)[d]	126.3 (90.5)	140.5 (76.1)
Vagifem®	118.5 (76.3)	209.3 (63.5)[d]	283.1 (26.7)[d]	121.8 (95.3)	149.9 (83.1)[d]

Source: Adapted from sNDA 20-908/SE2-013, Summary of Clinical Safety Studies, Table 3-2 on page 32 of 46 and Tables 303 and 3-4 on page 33 of 46.
a. Values are Geometric Mean in pg/mL (Geometric % CV).
b. Day 82 = 3 days since last treatment following 10 weeks of twice-weekly administration.
c. Day 83 = last administration of study medication.
d. Statistically significantly higher than Day -1.
e. Statistically significantly lower than Day -1.

Medical Officer's Comments:

As shown in Table 29, the highest estradiol levels were observed on the first dosing day (day 1) for both the 10 mcg estradiol vaginal tablet and Vagifem® 25 mcg treatment groups. Overall, mean plasma estradiol levels were consistently lower for the 10 mcg estradiol vaginal tablet treatment group compared to the Vagifem® 25 mcg treatment group. In addition, the mean $C_{ave(0-24)}$ values were below 20 pg/mL for all subjects in the 10 mcg estradiol vaginal tablet treatment group at each assessment day in this 12-week study. As shown in Table 24, this was not the case for the Vagifem® 25 mcg treatment group, however. Table 29 also shows that the mean estrone and estrone sulfate values returned to near baseline levels at days 82 and 83 for the 10 mcg estradiol vaginal tablet treatment group.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In this submission, the safety population included all randomized subjects who received at least 1 dose of study medication. During the 52-week Study VAG-2195, 308 subjects were included in the safety population (205 subjects in the 10 mcg estradiol vaginal tablet treatment group and 103 subjects in the placebo vaginal tablet treatment group). During the 12-week Study VAG-1850, 57 subjects were included in the safety population (29 subjects in the 10 mcg estradiol vaginal tablet treatment group and 28 subjects in the Vagifem® 25 mcg treatment group).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

In this submission, the safety population included all randomized subjects who received at least 1 dose of study medication.

7.1.8.3 Standard analyses and explorations of vital signs data

Per the submission, there were no clinically relevant changes in any of the vital sign parameters (systolic and diastolic blood pressure and pulse) and weight for subjects in Study VAG-2195. Subject (b) (6) in Study VAG-1850 in the 10 mcg estradiol vaginal tablet treatment group developed hypertensive values and was referred to her primary care practitioner who started her on antihypertensive treatment with beta blocker after day 58 of study participation. Subject (b) (6) completed Study VAG-1850. No additional analysis of vital signs data was performed by the reviewer.

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data was performed by the reviewer.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Electrocardiograms were not obtained Phase 3a Study VAG-2195.

During the conduct of Study VAG-1850, Subject (b) (6) in the Vagifem® 25 mcg treatment group was found to have an asymptomatic cardiac arrhythmia during visit 5 (week 8). A cardiologic examination including a long term ECG showed a cardiac arrhythmia with intermittent atrial fibrillation and ventricular extra systoles. Treatment with a beta blocker was started. Subject (b) (6) completed Study VAG-1850.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and exploration of ECG data were performed or conducted.

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

No QT or QT_c interval data is included in the submission. No cases of Torsades de pointes or ventricular tachycardia were reported in the safety data.

7.1.10 Immunogenicity

No human immunogenicity studies, data, or published literature were submitted with the sNDA.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under IND (b)(4) for 10 mcg estradiol vaginal tablets. No data or published literature was submitted with the sNDA on human carcinogenicity.

Currently, the Agency recommends that the following information be included in estrogen class labeling: "Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver."

7.1.12 Special Safety Studies

No special safety studies were conducted during the drug development program for 10 mcg estradiol vaginal tablets.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Per the submission, there were no cases of overdose with the study medication in the clinical development program of 10 mcg estradiol vaginal tablets.

7.1.14 Human Reproduction and Pregnancy Data

Given that the indication being sought in sNDA 20-908/SE2-013 is the (b)(4) no formal studies in humans on the effects of 10 mcg estradiol vaginal tablets in human reproduction or pregnancy were performed.

7.1.15 Assessment of Effect on Growth

10 mcg estradiol vaginal tablets have not been tested in pediatric subjects.

7.1.16 Overdose Experience

No cases of overdose with 10 mcg estradiol vaginal tablets have been reported during the drug development program.

7.1.17 Postmarketing Experience

Vagifem® (estradiol vaginal tablets) 25 mcg was approved in 1999 for the treatment of atrophic vaginitis.

The Division of Adverse Event Analysis (DAEA) was consulted for a safety review for Vagifem®. Per the consultation, the term "data mining" refers to the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences (i.e., "signals") in large databases. These signals can then be evaluated for intervention as appropriate. The WebVDME data mining application from Lincoln Technologies was searched on February 14, 2008 using the trade name "Vagifem". In addition, the Adverse Event Reporting System (AERS) was searched. AERS "s a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. FDA receives adverse drug reaction reports from manufacturers as required by regulation, including foreign and domestic reports. Health care professionals and consumers send reports voluntarily through the MedWatch program. Based on data entry rules, the adverse events reports are entered into the AERS database. All reported adverse event terms are coded using a standardized international terminology, MedDRA (Medical Dictionary for Regulatory Activities)."

"A search of the AERS database for any report with the suspect drug Vagifem listed as the Trade name retrieved 188 cases. The commonly reported preferred term (PT) is listed below:

Preferred Term (PT)	**Count of PTs**	**Percent of Total**
Breast Cancer Female	85	45.21%
Breast Cancer	19	10.11%
Pain	14	7.45%
Anxiety	11	5.85%
Estrogen Receptor Assay Positive	6	3.19%
Progesterone Receptor Assay Positive	6	3.19%
Urticaria	6	3.19%
Psychiatric Symptom	5	2.66%
Vaginal Hemorrhage	5	2.66%

These events were compared against the current approved labeling; the only unlabeled events are anxiety and psychiatric symptom."

"The term psychiatric symptom is too non-specific to be meaningful. Eleven reports of anxiety were retrieved, which is not particularly noteworthy because anxiety disorders are the most common class of psychiatric disorders. Thus, the searches of the AERS database did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling."

Medical Officer's Comments:

The DAEA consult confirmed that a search of the AERS database for Vagifem® did not identify any adverse events for consideration as additions to the proposed labeling. DAEA had no labeling recommendations based on the postmarketing safety review completed.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 "Tables of Clinical Studies" in this review summarizes the single Phase 3a clinical trial submitted to support the efficacy of the 10 mcg estradiol vaginal tablet. Primary Phase 3a Study VAG-2195 was used in the evaluation of safety and efficacy. This study contributed an adequate representation for postmenopausal women.

Phase 1 Study VAG-1850 provided additional safety data.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 "Tables of Clinical Studies" for the clinical trials conducted. This table summarizes the study design and number of subjects in each treatment group.

7.2.1.2 Demographics

The following two tables show the demographic characteristics for the ITT population in Study VAG-2195 and Study VAG-1850.

Table 30: Subject Demographic and Baseline Characteristics in Study VAG-2195

Characteristic	**10 mcg Estradiol Vaginal Tablet**	**Placebo Vaginal Tablet**
Numbers Randomized	205	104
Age (years) Mean (SD) [Range]	57.5 (5.64) [46-81]	57.7 (5.27) [46-75]
Race (n) Asian/Black/White/Other	2/6/192/5	3/4/95/2
BMI (kg/m^2) Mean (SD) [Range]	25.2 (3.5) [18-35]	24.9 (4.3) [18-35]
Time Since Last Menses (years) Mean (SD) [Range]	8.0 (5.8) [1-32]	8.2 (5.3) [1-29]

Source: Adapter from sNDA 20-908/SE2-013, Summary of Clinical Safety Studies, Table 1-5, page 9 of 46.

Table 31: Subject Demographic and Baseline Characteristics in Study VAG-1850

Characteristic	**10 mcg Estradiol Vaginal Tablet**	**Vagifem® 25 mcg**
Numbers Treated	29	28
Age (years) Mean (SD) [Range]	65.4 (2.6) [60-70]	65.1 (3.2) [60-70]
Race (n) White	29	28
Weight (kg) Mean (SD) [Range]	65.2 (9.1) [47.6-84]	67.3 (10.3) [53.7-97]
BMI (kg/m^2) Mean (SD) [Range]	24.9 (3.1) [18.5-29.9]	25.2 (3.0) [19.8-30]
Hysterectomy (yes/no)	0/29	0/28

Source: Adapter from sNDA 20-908/SE2-013, Summary of Clinical Safety Studies, Table 1-6, page 10 of 46.

Medical Officer's Comments:

Overall, the treatment groups in Study VAG-2195 and in Study VAG-1850 were similar with respect to demographics and baseline characteristics.

7.2.1.3 Extent of exposure (dose/duration)

A total of 308 subjects received at least 1 dose of study medication and were included in all safety analysis in 52-week Study VAG-2195. Descriptive statistics for the extent of exposure are presented in Table 32.

Table 32: Duration of Exposure in Study VAG-2195

Duration	**10 mcg Estradiol Vaginal Tablet (N – 205)**	**Placebo Vaginal Tablet (N – 104)**
Duration of Treatment (days) Mean (SD) [Range]	317.7 (102.7) [2-400]	281.4 (132.7) [7-455]
N (%) Subjects Treated: ≤ Week 2 Week 3 – Week 12 Week 13 – Week 26 Week 27 – Week 40 Week 41 – Week 52 ≥ Week 52	 6 (2.9) 9 (4.4) 12 (5.8) 11 (5.4) 111 (54.1) 56 (27.3)	 4 (3.9) 15 (14.6) 6 (5.8) 5 (4.8) 47 (45.6) 26 (25.2)

Source: Adapter from sNDA 20-908/SE2-013, Summary of Clinical Safety Studies, Table 1-3, page 8 of 46.

In 12-week Study VAG-1850, 56 of the 57 treated subjects completed the study. Subject (b)(6) in the Vagifem® 25 mcg treatment group was withdrawn from the study on day 7 due to non-compliance.

Medical Officer's Comments:

As shown in Table 32, the mean duration of treatment was greater in the 10 mcg estradiol vaginal tablet treatment group. A higher incidence of discontinuations was observed for the placebo vaginal tablet treatment group in 52-week Study VAG-2195 as compared with the 10 mcg estradiol vaginal tablet treatment group (32.7% versus 20.0%, respectively). Ineffective therapy was given as the reason for discontinuation in 10.6% of placebo-treated subjects as compared with 2.9% of the 10 mcg estradiol-treated subjects in Study VAG-2195. This finding is not unexpected, especially, in a 52-week placebo-controlled clinical trial being conducted for a VVA indication.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

See the discussion of non-IND Study VAG-1748 in Section 7.1 "Methods and Findings" and in Subsection 7.1.2 "Other Serious Adverse Events".

7.2.2.2 Postmarketing experience

Vagifem® (estradiol vaginal tablets) 25 mcg has been marketed since year 2000. Postmarketing safety information has been provided proactively by Novo Nordisk Inc. through annual report submissions and labeling updates.

7.2.2.3 Literature

The published literature has extensively documented the potential risk and benefits of estrogen and estrogen plus progestin therapy for the treatment of vasomotor symptoms and symptoms of vulvar and vaginal atrophy associated with the menopause. These publications have raised appropriate safety concerns regarding both dose and duration of hormone therapy for menopausal symptoms. See page 13 for the review of findings of the National Institutes of Health (NIH) Women's Health Initiative (WHI) studies.

7.2.3 Adequacy of Overall Clinical Experience

A total of 308 treated subjects participated in the Phase 3a Study VAG-2195. Fifty-seven treated subjects participated in 12-week Study VAG-1850.

Medical Officer's Comments:

Overall, the total number os subjects participating in 52-week Study VAG-2195 and 12-week Study VAG-1850 provided adequate safety information for the 10 mcg estradiol vaginal tablet.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required for the 10 mcg estradiol vaginal tablet. It is recognized that long-term continuous administration of estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes, and liver.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing conducted in Study VAG-2195 and Study VAG-1850, and the efforts to elicit adverse event data, were adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Section 5 of this review gives a brief summary of the clinical pharmacology for estradiol. See the Clinical Pharmacology and Pharmacokinetics Review for a more complete discussion. The metabolism and excretion of estrogen drug products are sufficiently understood to address in the label potential safety concerns in patients with impaired excretory or metabolic function and problems resulting from drug-drug interactions.

In vitro and in vivo studies of other estrogen drug products have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations, phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effect and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. No further testing for these previously well defined drug interactions with estradiol are required.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The gynecologic safety data submitted is generally adequate. Novo Nordisk was requested to provide additional safety information regarding the endometrium. The Applicant responded promptly with the requested information. The safety data submitted with the sNDA and the additional information provided by the Applicant upon request of the Agency were sufficiently adequate for the evaluation of potential adverse events.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the safety data submitted with sNDA 20-908/SE2-013 for the safety cohort of 308 postmenopausal women with uteri was adequate. Phase 3a, 12-month Study VAG-2195 fulfills the Agency's requirement to conduct a 12-week, double-blind, placebo-controlled safety and efficacy study for the (b)(4) The full 52-weeks of Study VAG-2195 were double-blind and placebo-controlled. In addition, Study VAG-2195 provided safety data regarding the use of unopposed estrogen in a woman with a uterus over a 12 month treatment duration.

7.2.9 Additional Submissions, Including Safety Update

A 4-Month Safety Update was submitted on April 3, 2008 which included the following information:

- "VAG-1850 – no new or follow-up safety information as of 13 March 2008."
- "VAG-2195 – no new safety information; follow-up safety information only for four subjects/five cases as of 13 march 2008."

The 4-Month Safety Update also provided initial serious adverse events from an ongoing non-IND European safety trial, VAG-1748, being "conducted as per CHMP guidelines in support of the registration of Vagifem 10 µg tablets in Europe."

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-related adverse events have been discussed previously in Section 7.1.3 "Dropouts and Other Significant Adverse Events", Subsection 7.1.3.3 "Other significant adverse events". Refer to these subsections for information on selected drug-related adverse events.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The reported safety data for 52-week Study VAG-2195 and 12-week Study VAG-1850 for the 10 mcg estradiol vaginal tablet was individually evaluated.

7.4.1.1 Pooled data vs. individual study data

The reported safety data for 52-week Study VAG-2195 and 12-week Study VAG-1850 for the 10 mcg estradiol vaginal tablet was individually evaluated.

7.4.1.2 Combining data

No data was combined in the submission.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The issue of dose dependency of reported adverse events has been discussed in several sections of this review, particularly in Section 7.1.2 "Other Serious Adverse Event", and Section 7.1.3 "Dropouts and Other Significant Adverse Events".

7.4.2.2 Explorations for time dependency for adverse findings

Exploration of time-dependent adverse event in 12-month Study VAG-2195 did not demonstrate any positive associations. The use of unopposed estrogen in a woman with a uterus increases the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. One case of endometrial cancer was reported in Study VAG-2195. See Subsection 7.1.3.3 "Other significant adverse events", Endometrial Biopsy, for information for Subject (b)(6) diagnosed with adenocarcinoma with FIGO Grade 2.

Medical Officer's Comments:

One additional subject in Study VAG-2195(Subject (b)(6) treated with 10 mcg estradiol vaginal tablet) was diagnosed with complex hyperplasia without atypia on study day 43. Subject (b)(6) reportedly took study medication for 9 days. Per the information provided, the screening endometrial biopsy specimen for Subject (b)(6) was reported as polyps (specimen obtained on day -37 (b)(6)]). Three separate, blinded pathologists examined the baseline endometrial sample. Pathologist 1 reported an inactive endometrium. Pathologist 2 reported an inactive endometrium and atrophic type polyp. Pathologist 3 reported inactive to weak proliferation. Because there was no agreement between the three pathologists, the most severe pathologic diagnosis (atrophic polyp) became the final baseline diagnosis. Subject (b)(6) end-of-study endometrial biopsy (specimen obtained on (b)(6)) was reported as complex hyperplasia without atypia (Pathologist 1 reported inactive to weak proliferation, Pathologist 2 reported complex hyperplasia without atypia, and Pathologist 3 reported limited endometrium with focal

area of glandular crowding without cytologic atypia). The reported baseline endometrial biopsy findings and the causality of complex hyperplasia without atypia in Subjec[redacted](b)(6) is questionable.

7.4.2.3 Explorations for drug-demographic interactions

No drug-demographic interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

7.4.2.4 Explorations for drug-disease interactions

Per the submission, no drug-disease interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were studied in the 10 mcg estradiol vaginal tablet clinical development program.

7.4.3 Causality Determination

See Subsection 7.1.3.3 "Other Significant Adverse Events" for information regarding endometrial thickness (page 65) and endometrial biopsy (page 67) and 10 mcg estradiol vaginal tablets use.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

For the [redacted](b)(4), the Applicant requested approval of the 10 mcg estradiol vaginal tablet administered daily for 2 weeks followed by twice-weekly administration.

8.2 Drug-Drug Interactions

No drug-drug interactions studies were performed as part of the 10 mcg estradiol vaginal tablet development program.

8.3 Special Populations

No pharmacokinetic studies were conducted in special populations, including subjects with renal or hepatic impairment.

Based on data from comparable estrogen therapy products, no formal studies in humans on the effect of 10 mcg estradiol vaginal tablet on reproduction or pregnancy were performed. Similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified.

8.4 Pediatrics

Estradiol vaginal tablet 10 mcg is not indicated for use in a pediatric population.

8.5 Advisory Committee Meeting

There was no advisory committee meeting in which 10 mcg estradiol vaginal tablet was discussed.

8.6 Literature Review

Literature relevant to estrogen therapy has been referenced in this review as needed. There is no need for a separate comprehensive review of the literature.

8.7 Postmarketing Risk Management Plan

There is no need for a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no relevant materials that are not included in other sections of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

The reviewer does not recommend approval of the 10 mcg estradiol vaginal tablet for the (b)(4) . Sufficient evidence was not provided in the application to conclude that the 10 mcg estradiol vaginal tablet inserted vaginally daily for two weeks followed by twice-weekly insertions provided relief in the treatment of (b)(4) (b)(4) when compared to placebo. The safety of the 10 mcg estradiol vaginal tablet was not a major concern. The reported serious and common adverse events are consistent with other intravaginal estrogen hormone products approved to (b)(4) .

9.2 Recommendation on Regulatory Action

sNDA 20-908/SE2-013 is not recommended for approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No Phase 4 clinical study commitment is proposed.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

No labeling review has been completed. sNDA 20-908/SE2-013 is not recommended for approval.

9.5 Comments to Applicant

(b)(4)

Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", recommends that one or more 12-week, randomized, double-blind, placebo-controlled clinical trials be conducted that evaluate three co-primary endpoints. The mean change from baseline to week 12 in the moderate to severe self-assessed symptom identified by the subject as being the most bothersome to her is one of the three recommended co-primary endpoints. Phase 3a Study VAG-2195 did not demonstrate a statistically significant difference versus placebo for any of the following vaginal symptoms: dryness, irritation/itching, soreness, dysuria, pain associated with sexual activity, or bleeding associated with sexual activity.

APPENDICES

9.6 Review of Individual Study Reports

The review of the single Phase 3a Study VAG-2195 is included in this review. The review of Phase 1 Study VAG-1850 is included in this review

9.7 Line-by-Line Labeling Review

No labeling review has been completed. sNDA 20-908/SE2-013 is not recommended for approval.

REFERENCES

1. Rossouw, JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. JAMA. 2007;297:1465-1477.

2. Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. Arch Int Med. 2006;166:357-365.

3. Curb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a uterus. Arch Int Med. 2006;166:772-780.

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5. Heiss G, et al. Health Risks and Benefits 3 Years After Stopping Randomized Treatment With Estrogen and Progestin. JAMA. 2008;299:1036-1045.

6. Jackson RD, et al. Effects of conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. J Bone Miner Res 2006;21:817-828.

7. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. Circulation. 2006;113:2425-2434.

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/s/

Theresa Van Der Vlugt
10/6/2008 06:26:10 PM
MEDICAL OFFICER

Shelley Slaughter
10/8/2008 03:17:26 PM
MEDICAL OFFICER
I concur with Dr. van der Vlugt's recommendation that approval not be granted for the 10mcg estradiol vaginal tablet. The rationale for my concurrence and minor differences between the primary and secondary reviews are presented in the CDTL review.

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/s/

Theresa Van Der Vlugt
2/7/2008 06:45:35 PM
MEDICAL OFFICER

Shelley Slaughter
2/8/2008 10:01:18 AM
MEDICAL OFFICER
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

PRODUCT QUALITY REVIEW(S)

Office of New Drug Quality Assessment
Chemistry Review for Clinical Division, HFD-580

ADDENDUM TO CHEMISTRY REVIEW OF 20-908 SE2 013

This addendum provides clarification as follows:

Efficacy supplement 20-908 SE2 013 provides for an additional lower strength Vagifem tablet, 0.010 mg estradiol, to be manufactured at a new drug product manufacturing site, Novo Nordisk in Maaloev, Denmark.

Efficacy supplement 20-908 SE2 013 was found to be acceptable from a chemistry, manufacturing and controls (CMC) perspective in the first review cycle. See chemistry review #1 by Dr. J. Salemme. The supplement received a Complete Response for Clinical reasons.

Responses to the Complete Response were submitted 26-May-2009. Revised carton and container labels were submitted 30-Oct-2009. Chemistry review #2 by Dr. Salemme found the revised carton and container labels to be acceptable.

This addendum clarifies that the responses to the Complete Response did not provide any new CMC information for review.

Therefore, based on the evaluation of the submission as shown in Chemistry review #1, and the evaluation of the revised carton and container labeling as shown in Chemistry review #2, efficacy supplement 20-908 SE2 013 is recommended for Approval from a CMC perspective.

_____

Chemistry Reviewer: Dr. J. Salemme
Date: 18-Nov-2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

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/s/

JEAN SALEMME
11/18/2009

HASMUKH B PATEL
11/19/2009

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF POST-MARKETING EVALUATION
Review of NDA 20-908 SE2 013
for Clinical Division, HFD- 580

CHEMIST REVIEW #2
OF **EFFICACY SUPPLEMENT**

1. **ORGANIZATION**: ONDQA-DPE
2. **NDA NUMBER:** 20-908 SE2-013
3. **SUPPLEMENT DATES:**
   Letter/Stamp Date: 7-Dec-2007
   Original **Due Date:** 7-Oct-2008
   Resubmission Due Date: 5-Oct 2009
4. **AMENDMENT: 18-Sept-2009**
5. **RECEIVED BY CHEMIST** Dec 2007

6. **SPONSOR NAME AND ADDRESS**
   Novo Nordisk Inc.
   Princeton, NJ

7. **SUPPLEMENT PROVIDES FOR:** a lower strength, 0.010 mg estradiol, drug product

8. **DRUG PRODUCT NAME:** Vagifem
9. **NONPROPRIETARY NAME:** Estradiol Vaginal Tablets
10. **DRUG SUBSTANCE:** Estradiol
11. **DOSAGE FORM/STRENGTH** Tablet, 0.025 mg
12. **ROUTE OF ADMINSTRATION:** Vaginal
13. **INDICATION:** (b)(4)
14. **HOW DISPENSED:** Rx
15. **RELATED IND/NDA/DMF:** NDA 20-908 S-014

16. **COMMENTS:**
    This efficacy supplement proposes an additional lower strength tablet, 0.010 mg estradiol, to be manufactured at a new drug product manufacturing site, Novo Nordisk in Maaloev, Denmark. The supplement was not approved first cycle. See Medical Officer review.

    Chemistry review #1 recommended the supplement for approval based on CMC information. The supplement was not approved first cycle based on Clinical evaluation. Chemistry review #2 of this supplement evaluates the container and carton labeling. The DMETS reviewer provided comments regarding the container and carton, which the sponsor addressed.

17. **CONCLUSION**
    The carton and container labeling is acceptable from a CMC perspective.

18. **REVIEWER NAME**	**DATE COMPLETED**
J. Salemme, Ph.D., Chemistry reviewer, ONDQA-DPE	2-Nov-2009

PM: G. Lyght, HFD-580, Project Manager
Reviewed: Dr. Hasmukh Patel, Branch Chief, ONDQA-DPE

Review Notes

Chemistry review #1 recommends this supplement for approval from a CMC perspective. See Chemistry review #1. The supplement was not approved first cycle due to Clinical evaluation.

Chemistry review #2 evaluates the carton and container labels, and provides the sponsor's responses to the DMEPA label comments.

Amendment September 2009
This amendment provides the draft labels and labeling for Vagifem 10 mcg as recommended by DMEPA.

Comments from the DMEPA reviewer are shown below in italic font with the sponsor's response below each comment.

1. *Replace all unit designations expressed as "µg" with "mcg" when expressed with a strength to be consistent with FDA's policy on excluding dangerous abbreviations and symbols from approved labels and labeling. FDA launched a campaign on June 14, 2006 warning health providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g. trailing zeros).*

   The unit designation "µg" has been replaced in all labels and labeling with "mcg".

2. *Consider revising the carton labeling so that the* (b)(4) *In its current location it may be more difficult to locate the* (b)(4) *because it is inconsistent from what consumers and healthcare practitioners are used to.*

   The enclosed carton labeling has been revised to move (b)(4)

3. *List the inactive ingredients on the carton labeling per 21 CFR 201.100(b)(5).*

   The inactive ingredients are now listed on the enclosed carton labeling.

4. *The numbering in the patient labeling for the instructions is confusing in presentation and the figures are not coordinated with the text. Consider labeling figures alphabetically and reserve the numbers for the instruction steps.*

   The instructions in the patient labeling have been revised and the figures are listed alphabetically with numbers for the instruction steps.

The modified label and carton were provided to DMEPA by the Clinical Division Project Manager, G. Lyght, and are acceptable. Additionally, as shown above, the sponsor has amended the labeling according to the DMEPA reviewer comments.

Evaluation: Acceptable.

LABELING [2-Nov-2009 amendment]

The HOW SUPPLIED, DOSAGE AND ADMINISTRATION, and DOSAGE FORMS AND STRENGTHS sections of the label have been amended to add information pertaining to the 10 mcg dose.

HOW SUPPLIED

Each Vagifem (estradiol vaginal tablets), 10 mcg and 25 mcg, is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contain 8 or 18 applicators with inset tablets.

Vagifem 25 mcg
8 applicators: NDC 0169-5173-03
18 applicators: NDC 0169-5173-04

Vagifem 10 mcg
8 applicators: NDC 0169-5176-03
18 applicators: NDC 0169-5176-04

DOSAGE AND ADMINISTRATION

Vagifem should be administered intravaginally:

- 1 tablet daily for 2 weeks, followed by 1 tablet twice weekly (for example, Tuesday and Friday).

DOSAGE FORMS AND STRENGTHS

(b)(4)

CONTAINER LABEL AND CARTON

Container Label

The proposed container label is the following:

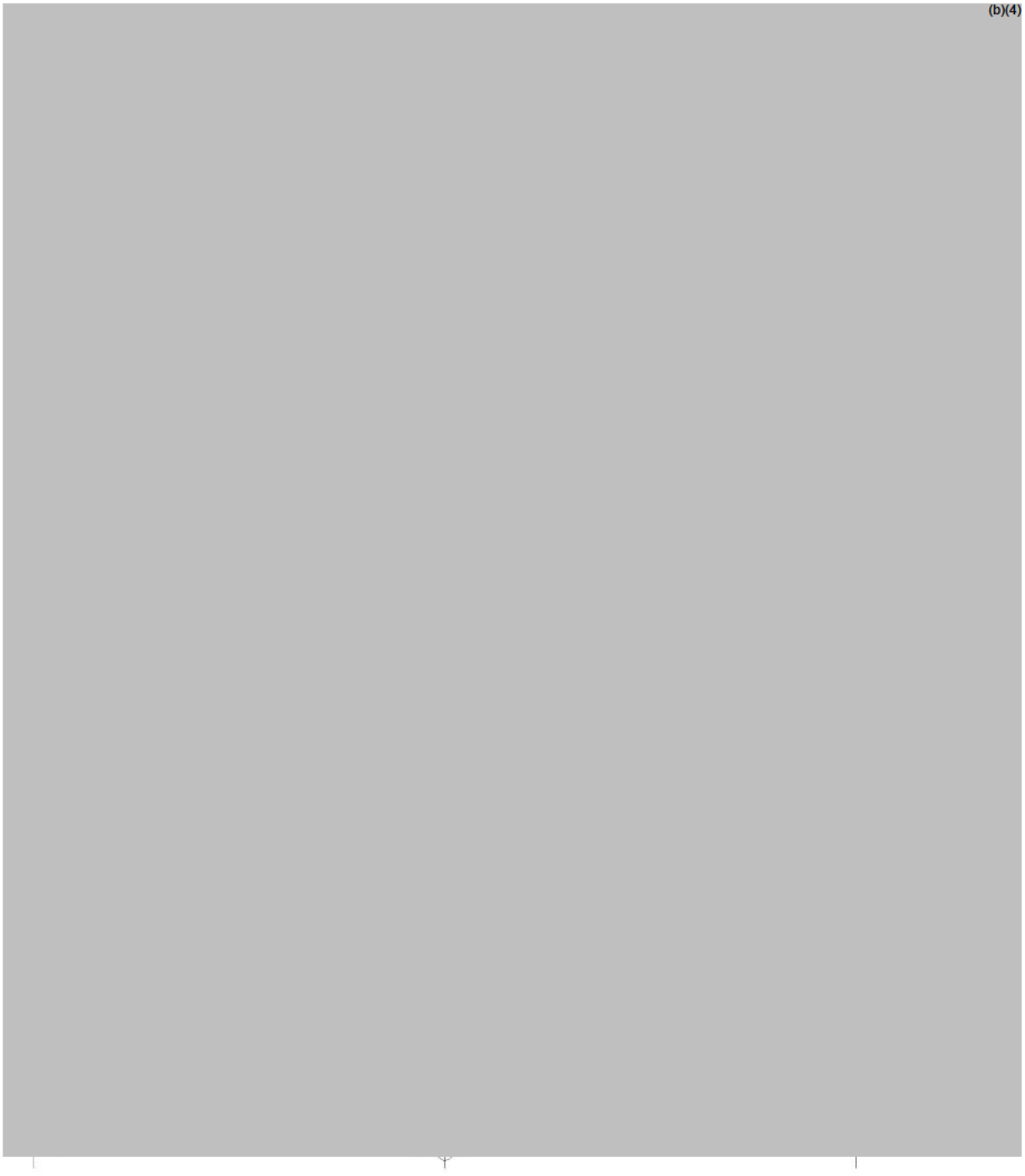
Carton [amendment of 2-Nov-2009]

Initially, the proposed carton showed a (b)(4). The Medical Officer in HFD-580, Dr. S. Slaughter, agreed with the CMC evaluation that the (b)(4). In response to the Division's request, the sponsor amended the carton to remove the (b)(4) and to provide the following text:

- 1 tablet daily for 2 weeks, followed by 1 tablet twice weekly (for example, Tuesday and Friday)

.

The proposed carton is shown on the next page.



Evaluation of labeling: Acceptable from a CMC perspective.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

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/s/

JEAN SALEMME
11/02/2009

HASMUKH B PATEL
11/03/2009

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF POST-MARKETING EVALUATION
Review of NDA 20-908 SE2 013
for Clinical Division, HFD- 580

CHEMIST REVIEW
OF **EFFICACY SUPPLEMENT**

1. **ORGANIZATION**: ONDQA-DPE
2. **NDA NUMBER:** 20-908 SE2-013
3. **SUPPLEMENT DATES:**
   Letter/Stamp Date: 7-Dec-2007
   Due Date: 7-Oct-2008
4. **AMENDMENT:** 28-Aug-2008
5. **RECEIVED BY CHEMIST** Dec 2007

6. **SPONSOR NAME AND ADDRESS**
   Novo Nordisk Inc.
   Princeton, NJ

7. **SUPPLEMENT PROVIDES FOR:** a lower strength, 0.010 mg estradiol, drug product manufactured at a new drug product manufacturing site, Novo Nordisk, C2 site in Maaloev, Denmark

8. **DRUG PRODUCT NAME:** Vagifem
9. **NONPROPRIETARY NAME:** Estradiol Vaginal Tablets
10. **DRUG SUBSTANCE:** Estradiol
11. **DOSAGE FORM/STRENGTH** Tablet, 0.025 mg
12. **ROUTE OF ADMINSTRATION:** Vaginal
13. **INDICATION:** (b)(4)
14. **HOW DISPENSED:** Rx
15. **RELATED IND/NDA/DMF:** NDA 20-908 S-014, (approvable action April 2008)

16. **COMMENTS:**
This efficacy supplement proposes an additional lower strength tablet, 0.010 mg estradiol, to be manufactured at a new drug product manufacturing site, Novo Nordisk in Maaloev, Denmark, with a scale-up in batch size from (b)(4) to (b)(4), with most of the approved chemistry, manufacturing and controls. The approved methods for identification, assay, related substances, and dissolution have been modified and validated for the analysis of both the 0.025 mg and the 0.010 mg tablets.

Batch release and stability data to 24 months/25C/60% RH, to 12 months/30C and to 6 months/40C are provided for three production batches manufactured at the proposed Maaloev Denmark site. The data show that the 0.010 mg batches meet the approved drug product specification and are comparable to the approved tablets. The Office of Compliance finds the proposed site acceptable.

Two clinical studies have been evaluated by the Clinical Division, HFD-580, to support the lower 0.010 mg strength tablet: bioavailability study VAG-1850 and efficacy study

VAG- 2195. Both studies used 0.010 mg tablets manufactured at the proposed C2 site. The studies were found to be acceptable from a Clinical Biopharmaceutics perspective.

Responses to an Information Request are acceptable. See review.

17. CONCLUSIONS AND RECOMMENDATIONS

Adequate information has been provided to support this supplement. Additionally, the Office of Compliance recommends the proposed manufacturing site for approval. This supplement, therefore, is recommended for approval.

Action Item: Issue an Approval Letter.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., Chemistry reviewer, ONDQA-DPE	4-Sept-2008

PM: G. Lyght, HFD-580, Project Manager
Reviewed: Dr. Hasmukh Patel, Branch Chief, ONDQA-DPE

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/s/

Jean Salemme
9/18/2008 04:33:59 PM
CHEMIST

Hasmukh Patel
9/19/2008 09:45:50 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

NON-CLINICAL REVIEW(S)

NDA: 20-908/S-013

Date: November 9, 2009

Sponsor: Novo Nordisk Pharmaceuticals, Inc.

Drug: Vagifem (estradiol vaginal tablets) 10 ug

Application date: May 26, 2009

This resubmission is a response to the Division's action letter of October 15, 2008. There are no new pharm/tox data or information that was not previously reviewed in the original pharm/tox NDA review of May 21, 2008.

Conclusion: The resubmission contains no new pharm/tox information and the original pharm/tox recommendation for approval of Vagifem 10 ug is unchanged.

Alex Jordan, PhD

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

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/s/

ALEXANDER W JORDAN
11/09/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	s**20-908**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**Dec. 7, 2007**
PRODUCT:	**Vagifem (estradiol vaginal tablets) 10 ug**
INTENDED CLINICAL POPULATION:	postmenopausal women (b)(4) (b)(4)
SPONSOR:	**Novo Nordisk, Inc**
DOCUMENTS REVIEWED:	Novo Nordisk has referenced the non-clinical pharmacology/toxicology information contained in NDA 20-908, Vagifem (estradiol vaginal tablet) 25 ug. Therefore, no new pharmacology, toxicology or pharmacokinetic/toxicokinetic studies were necessary to support the current NDA 20-908 application.
REVIEW DIVISION:	**DRUP**
PHARM/TOX REVIEWER:	**Alex Jordan**
PHARM/TOX SUPERVISOR:	**Lynnda Reid**
DIVISION DIRECTOR:	**Scott Monroe**
PROJECT MANAGER:	**George Lyght**

Date of review submission to Division File System (DFS): 5/21/2008

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Pharmacology recommends approval of Vagifem (estradiol vaginal tablets) 10 ug.

B. Recommendation for nonclinical studies None

C. Recommendations on labeling Labeling will be similar to Vagifem (estradiol vaginal tablets) 25 ug approved under NDA 21-840, which has the same formulation composition and dosing schedule and is used for the same indication.

II. Summary of nonclinical findings

Brief overview of nonclinical findings:

No new toxicology studies were submitted and none are necessary.

A. Pharmacologic activity: estrogen

B. Nonclinical safety issues relevant to clinical use: None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 20-908
Review number: 1
Sequence number/date/type of submission: 000/12-7-07/Supplemental New Drug Application/ s013
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Novo Nordisk, Inc, Princeton, NJ.
Manufacturer for drug substance:

Reviewer name: Alex Jordan, PhD
Division name: DRUP

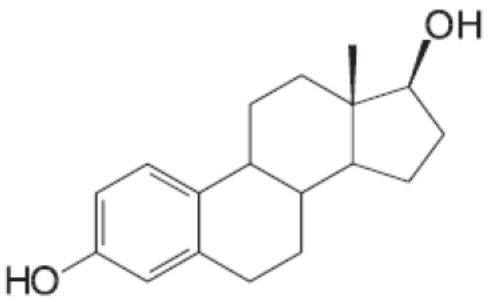
Review completion date:

Drug:

Trade name: Vagifem (estradiol vaginal tablet) 10 ug
Generic name: estradiol-17β
Code name:
Chemical name: Estradiol

CAS registry number: 797-63-7 (LNG); 57-36-6 (EE)
Molecular formula/molecular weight: $C_{21}H_{28}O_2$/312.45 (LNG); $C_{20}H_{24}O_2$/296.41 (EE)

Structure:



Relevant INDs/NDAs/DMFs: NDA 20-908

Drug class: estrogen

Intended clinical population: Postmenopausal women with (b)(4) (b)(4).

Clinical formulation:

Table 1 Composition

Name of Ingredients	Quantity mg/tablet[1]	Function	Reference to standards
Drug substance:			(b)(4)
Estradiol hemihydrate[2]	10.3 µg[3]	Active	
equivalent to		Substance	
estradiol (anhydrous)	10.0 µg		
Other ingredients:		(b)(4	
Hypromellose			
Lactose monohydrate			
Maize starch[7]			
Magnesium stearate			
Film-coating: (b)(4)			
Hypromellose (b)(4)			

Route of administration: vaginal

Dosing regimen: Initial dose: One tablet inserted vaginally, once daily for two weeks.
Maintenance dose: One tablet twice weekly.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data Reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 20-908 are owned by Novo Nordisk or are data for which Novo Nordisk has obtained a written right of reference. Any information or data necessary for approval of NDA 20-908 that Novo Nordisk does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Novo Nordisk does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 20-908.

Studies reviewed within this submission: No pharmacology/toxicology studies conducted or submitted. All studies refer to the approved Vagifem 25 ug tablets.

Studies not reviewed within this submission: None submitted

2.6.2 PHARMACOLOGY

Pharmacology of estradiol-17β is well established.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None submitted

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

None submitted

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None submitted

2.6.6 TOXICOLOGY

None submitted

2.6.7 TOXICOLOGY TABULATED SUMMARY

No new toxicology studies submitted. Safety is supported by reference to approved Vagifem (estradiol vaginal tablet) 25 ug.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on the approval of Vagifem (estradiol vaginal tablet) 25 ug, which has the same formulation and dosing schedule as Vagifem 10 ug, Pharmacology considers Vagifem (estradiol vaginal tablets) 10 ug safe for the proposed indication.

Unresolved toxicology issues (if any): None

Recommendations: Pharmacology recommends approval of sNDA 20-908 for Vagifem (estradiol vaginal tablets) 10 ug.

Suggested labeling: Labeling will be similar to that for Vagifem (estradiol vaginal tablets) 25 ug.

APPENDIX/ATTACHMENTS None

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/s/

Alexander W. Jordan
5/21/2008 08:51:00 AM
PHARMACOLOGIST

Lynnda Reid
5/21/2008 08:58:46 AM
PHARMACOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW OF CLASS 2 RE_SUBMISSION

CLINICAL STUDIES

NDA/Serial Number:	20-908/SE1-013
Drug Name:	Vagifem (estradiol) Vaginal Tablets, 10µg
Indication(s):	(b)(4)
Applicant:	Novo Nordisk Inc.
Date(s):	
Submission Date:	May 26, 2009
User Fee Goal Date:	November 26, 2009
Review Priority:	3S
Statistical Reviewer:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive & Urology Products
Clinical Team:	
Reviewer:	Theresa van der Vlugt, M.D.
Team Leader:	Shelley Slaughter, M.D.
Project Manager:	George Lyght

Keywords: Multiple Comparison, Analysis of Covariance (ANCOVA)

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study results support the efficacy of Vagifem (10 mcg estradiol vaginal tablets) in the treatment of atrophic vaginitis due to menopause. Treatment with Vagifem resulted in a statistically significant reduction in (1) a composite score of all most bothersome symptoms, (2) vaginal pH, (3) the percentage of parabasal cells compared to treatment with placebo at week 12. A statistically significant increase in superficial cells for treatment compared to placebo at week 12 was also demonstrated.

From a statistical perspective, the results demonstrate the efficacy of Vagifem 10 mcg in the treatment of atrophic vaginitis due to menopause.

1.2 Brief Overview of Clinical Studies

The conclusion was based on the data from one Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center study (VAG-2195). The objective of this study was to evaluate the efficacy and safety of the 10 mcg estradiol vaginal tablet in the treatment of postmenopausal atrophic vaginitis symptoms. Postmenopausal women with signs and symptoms of atrophic vaginitis and who met other inclusion/exclusion criteria were randomly assigned in a 2:1 ratio to receive either Vagifem 10 mcg or placebo.

The efficacy was evaluated by the following three co-primary endpoints:

(1) Mean change from baseline to week 12 in the composite score of all most bothersome vulvar and vaginal atrophy (VVA) symptoms.
(2) Mean change from baseline to week 12 in the vaginal maturation index (parabasal and superficial cells).
(3) Mean change from baseline to week 12 in the vaginal pH.

Note that in this resubmission, efficacy analysis of the first co-primary endpoint of change in all most bothersome symptoms (MBS) was based on a composite score of all symptoms as opposed to change in any individual most bothersome symptom score following an intent-to-treat principle.

1.3 Statistical Issues and Findings

In the original submission, the two statistical issues were use of appropriate statistical methods (parametric vs. non-parametric) and adjustment for multiplicity when one or more individual symptoms were the basis for the moderate to severe most bothersome co-primary endpoint.

In this resubmission, however, the sponsor reported efficacy results based on a composite score of all most bothersome symptoms using the intent-to-treat (ITT) principle. Therefore, unlike the original submission, the violation of distributional assumptions was no longer an issue and there

was no need for adjustment of type I error rate for multiplicity. We performed statistical analysis using an ANCVOVA model based on this ITT population and concluded that our results were similar to sponsor's results and did not find any other statistical issues with respect to sponsor's analysis.

In this resubmission, the sponsor was also requested to provide a re-analysis of the most bothersome symptoms composite score for the approved Vagifem 25 mcg drug product to demonstrate the change from baseline at week 7 and week 12 using last observation carried forward method. We verified these efficacy results which are summarized as follows:

(1) At week 12, treatment with Vagifem 10 mcg resulted in a statistically significant reduction in a composite score of all most bothersome symptoms, vaginal pH and the percentage of parabasal cells compared with patients treated with placebo at week 12. A statistically significant increase in the percentage of superficial cells compared with patients treated with placebo at week 12 was also demonstrated.

(2) At week 7 and week 12, treatment with Vagifem 25 mcg also demonstrated statistically significant reduction in a composite score of most bothersome symptoms.

2. INTRODUCTION

This re-submission is in response to Division's complete response letter, dated October 15, 2008 for original NDA 20-908. The letter indicated that the efficacy results based on FDA analysis did not demonstrate statistically significant reduction in any of the three pre-determined individual moderate to severe most bothersome symptoms. In a Type A meeting held in March 20, 2009, the sponsor argued that as per protocol the analysis should have been based on a composite score of all most bothersome symptoms using intent-to-treat (ITT) principle. The Division reconsidered the sponsor's pre-specified analysis plan and advised that the deficiencies in the letter could be addressed by re-analysis of the data as per protocol.

This submission contains the sponsor's result from the re-analysis of the efficacy data based on a composite score following ITT principle.

2.1. STATISTICAL EVALUATION

This review focuses on the re-analysis of the data on the efficacy of Vagifem 10 mcg dose evaluated in study VAG-2195, the source of database for the original submission and the updated efficacy data on the approved Vagifem 25 mcg.

In the original submission, we performed statistical analysis using two populations:mITT-1, (defined as all subjects who identified at baseline a moderate to severe most bothersome symptom and had a vaginal pH of >=5.0 and a vaginal cytology with <=5% superficial cells) and mITT-2 (all subjects in m-ITT-1 without consideration of pH and cytology). Using the mITT-1 population, our analyses indicated a p-value of 0.020 (non-parametric analysis) for dyspareunia, the only symptom that showed a p-value smaller than the nominal p-value of 0.05. After adjusting for multiple symptoms (3 symptoms), we concluded that treatment with Vagifem 10 mcg did not demonstrate statistically significant improvement for dyspareunia, compared to placebo. Similarly, using mITT-2 population, Vagifem 10 mcg did not demonstrate statistically significant improvement (p=0.116, ANCOVA on rank) compared to placebo.

2.2. Results

Most Bothersome Symptoms: In this resubmission, as noted earlier, the sponsor presented efficacy results (January 9, 2009 and May 26, 2009) based on a composite score using ITT population, defined as population consisting of patients who had a most bothersome vaginal symptom at baseline and had at least one post-baseline assessment of any MBS symptom. The sponsor's results showed a statistically significant (p=0.002) reduction from baseline to week 12 in the change in total score of all most bothersome symptoms in Vagifem 10 mcg treated patients compared to placebo.

However, the sponsor's efficacy result for change in MBS presented in the label was not consistent with what they have presented in their response. In the label, the number of analysis population shown was (b)(4) in placebo and Vagifem 10 mcg group) at baseline, as opposed to 283 (93 vs. 190 in placebo and vagifem group, respectively). The baseline mean should also be based on 283 patients as opposed (b)(4)

We performed statistical analysis using the sponsor's database of May 26, 2009 using 283 patients, a subset of 309 ITT populations. Our analysis method included ANCOVA model with treatment and baseline values as covariate using last-observation-carried-forward (LOCF) method for missing week 12 score.

Our results were similar to the sponsor's results. The mean reduction in total MBS symptoms score (-1.20 vs. -0.84 for Vagifem 10 mcg and placebo, respectively) was statistically significantly (p=0.002) higher for Vagifem 10 mcg treated patients compared to placebo treated patients. We made the necessary correction in the label to reflect the correct number of patients and the results.

Table 1: Mean Change from Baseline to Week 12 (LOCF) in Most Bothersome Symptoms[a] by Treatment Group – ITT Population[b]: StudyVAG-2195

	Vagifem 10 mcg N=190	**Placebo N=93**	**p-value***
Baseline Mean	2.36	2.29	-
Change[c]	-1.20	-0.84	0.002

[a] Symptoms were evaluated as 0=none, 1=Mild, 2=Moderate, 4=Severe.
[b] All randomized subjects who received at least one dose of study drug and had one most bothersome symptom at baseline and at least one post-baseline efficacy evaluation.
[c] Change from Baseline to Week 12 (LOCF)
* From ANCOVA with treatment effect and baseline values as a covariate in the model.
Data Source: Sponsor's resubmission dated May 26, 2009.

The label also included efficacy data for Vagifem 25 mcg in graphical format. To maintain consistency, as per Division's request, the sponsor submitted the updated results in tabular form along with the study (VAG-PD-9) dataset on November 17, 2009. We have verified their results which are summarized in Table 2. These results also demonstrate that Vagifem 25 mcg significantly reduced the composite score of symptoms at week 12 of treatment. Similar results were seen at week 7.

Table 2: Mean Change from Baseline in a Composite Score of Symptoms by Treatment Group – ITT Population: StudyVAG-PD-9

	Vagifem 25 mcg N=91	**Placebo N=47**	**p-value***
Baseline Mean	1.85	1.93	-
Change[a] at Week 7 (LOCF)	-1.22	-0.85	0.016
Change[a] at Week 12 (LOCF)	-1.33	-0.83	0.005

[a] Change from Baseline
* From ANOVA with center and treatment effect in the model.
Data Source: Sponsor's submission dated November 17, 2009.

Vaginal pH and Cytology: Using the same analysis population, there were also statistically significant reduction in vaginal pH and the percentage of parabasal cells among Vagifem 10 mcg

treated patients compared with placebo treated patients as shown in Table 3. Similarly, there was statistically significant increase in the percentages of superficial cells for Vagifem 10 mcg treated patients compared with placebo treated patients.

Table 3: Mean Change from Baseline to Week 12 (LOCF) in Vaginal Maturation Index and pH Score by Treatment Group – ITT Population: StudyVAG-2195

Parameter	Vagifem 10 mcg		Placebo		p-value*
	N	Mean	N	Mean	
Vaginal pH Score					-
Baseline	204	2.3	102	2.4	
Change[a]	202	-1.3	102	-0.4	<0.001
Parabasal Cells (%)					
Baseline	198	41.8	102	43.4	
Change[a]	195	-37.0	102	-9.3	<0.001
Superficial Cells (%)					
Baseline	198	3.3	102	2.5	<0.001
Change[a]	195	13.2	102	3.8	

[a] Change from Baseline to Week 12 (LOCF)
Data Source: Sponsor's resubmission dated January 9, 2009.

3. CONCLUSIONS

Based on the re-analysis of a composite score using ITT population, Vagifem 10 mcg demonstrated statistically significant improvement in all three co-primary endpoints, i.e., change in total most bothersome symptoms, vaginal pH and cytology compared to placebo.

The updated efficacy data on Vagifem 25 mcg also showed statistically significant reduction in a composite score of symptoms compared with placbo at week 7 and week 12.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

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/s/

MAHBOOB SOBHAN
11/20/2009

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-908
Drug Name:	Vagifem (estradiol) Vaginal Tablets, 10µg
Indication(s):	(b)(4)
Applicant:	Novo Nordisk Inc.
Date(s):	
Submission:	December 7th, 2007
Filing Meeting:	February 19 th, 2008
User Fee Goal Date:	October 7th, 2008
Review Priority:	Standard
Statistical Reviewer:	Shahla S. Farr, M.S.
Concurring Reviewers:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive & Urology Products
Clinical Team:	
Reviewer:	Theresa Van Der Vlugt, M.D.
Team Leader:	Shelly Slaughter, M.D.
Project Manager:	George Lyght

Keywords: Multiple Comparison, Rank Analysis of Covariance (ANCOVA)

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results do not support the efficacy of Vagifem (estradiol) Vaginal Tablets, 10µg in reducing the (b)(4) . The mean changes in the above three symptoms were not statistically significantly different for Vagifem treated patients compared to placebo patients after adjusting for multiplicity. The mean changes in other three co-primary endpoints, i.e., decrease in vaginal PH, decrease in the percentages of parabasal cells and increase in superficial cells were statistically significantly superior for Vagifem 10µg treated subjects than placebo treated subjects.

From a statistical perspective, the results do not demonstrate the efficacy of Vagifem 10µg in treating (b)(4) .

1.2 Brief Overview of Clinical Studies

The conclusion was based on data from one Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center study (VAG-2195). The objective of this study was to evaluate the efficacy and safety of Vagifem Low Dose (10 µg 17ß-estradiol vaginal tablet) in the treatment of postmenopausal atrophic vaginitis symptoms. Postmenopausal women with signs and symptoms of atrophic vaginitis and who met other inclusion/exclusion criteria were randomly assigned (2:1) to receive either Vagifem 10 µg or placebo.

The efficacy was evaluated by the following three co-primary endpoints:
(1) Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being most bothersome to her.
(2) Mean change from baseline to week 12 in the Vaginal Maturation Index and Value.
(3) Mean change from baseline to week 12 in the vaginal pH.

1.3 Statistical Issues and Findings

The Division reminded the sponsor at the phase 3 protocol development stage that the most bothersome co-primary endpoint must be based on at least one of the following symptoms: vaginal pain, vaginal bleeding, vaginal dryness, and irritation/itching rather than the composite of all five individual symptoms. Accordingly, the Division also recommended that the sample size must be adequate to test the most bothersome endpoint hypothesis. The sponsor addressed the above issues in this submission by analyzing the efficacy data as recommended, but failed to use appropriate statistical adjustment necessary for multiplicity.

In addition, the sponsor's use of ANCOVA model was not appropriate because of the violation of distributional assumption necessary for using such a model. In this review, our conclusions were based on non-parametric methods of analysis in modified intent-to-treat population who met all three FDA criteria.

2. INTRODUCTION

2.1 Overview

In this supplement, the applicant is seeking approval for a lower dose of Vagifem 10 µg estradiol, as opposed to currently approved dose of 25 µg estradiol vaginal tablets for the [redacted](b)(4). The submission contains s single study to support the lower strength.

The applicant addressed several design issues raised by the Division (communicated on November 15, 2007).

This data was submitted, completely, in eCTD format and is located at:
\\cdsesub1\evsprod\NDA020908

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

This study was performed in US (45 centers and 230 subjects) and Canada (4 sites and 79 subjects) and was randomized, double-blind, and parallel group study to investigate the efficacy and safety of Vagifem (estradiol) Vaginal Tablets, 10µg. Patients inserted one tablet intra-vaginally each day for 14 days, then one tablet twice weekly for the remaining 10 weeks.

Although the duration for this study was for 52 weeks, requirements from the regulatory agencies in Europe and the United States mandate that efficacy evaluations for any therapeutic hormonal agent must demonstrate statistically significant improvement when compared to placebo after 12 weeks of treatment. Thus, conclusions regarding treatment benefits were drawn over a 12 week treatment period.

***Primary Efficacy Endpoint*:** Originally, **t**he primary efficacy endpoints were as follows:
(1) Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being most bothersome to her
(2) Mean change from baseline to week 12 in the Vaginal Maturation Index and Value
(3) Mean change from baseline to week 12 in the vaginal pH.

However, as per Division's draft guidance, the sponsor was required to demonstrate the improvement in the most bothersome symptoms based on in at least one of the following three symptoms:
1) Vaginal Dryness
2) Vaginal Irritation
3) Vaginal Pain during Intercourse (Dyspareunia).

The analysis was to be limited to patients who had a vaginal pH > 5.0, had less than 5% superficial cells on the vaginal smear, and reported one vaginal symptom that was moderate to severe and most bothersome.

***Sample size*:** The original protocol had plan to randomize a total of 600 subjects (Vagifem 10 µg: 400 patients, placebo: 200 patients) into the trial. Based on sponsor's calculations, 600 subjects were adequate to test the superiority hypothesis with regards to three objective co-primary endpoints: vaginal PH, superficial cells and parabsal cells. But the protocol did not specify whether this sample size was also adequate to test for most bothersome endpoint or not.

Subsequently, in an amendment (serial # 068), the protocol made a change to reduce the sample size from 600 to 300 patients (Vagifem 10 µg: 200 patients, placebo: 100 patients). This change was made due to slow patient enrolment. Based on the sponsor's calculations, 300 subjects would provide 90% power to detect a difference of 0.48 in change from baseline to Week 12 for the relief of urogenital symptoms, composite index (based on the most bothersome symptom score of dryness, irritation/itching, soreness, dysuria, pain associated with sexual activity, and bleeding associated with sexual activity), with an estimated standard deviation of 1.1 in change from baseline to 12 weeks.

Statistical Methodology: The statistical analysis method that the sponsor used included use of Analysis of Covariance (ANCOVA) for the between group comparison in analyzing the most bothersome symptoms data, with treatment as a fixed effect and corresponding baseline value as a covariate. These analyses were performed on change from baseline scores at week 2, week 4, week 8, week 12, week 12 (LOCF). However, since the data was not normally distributed, this parametric analysis was not suitable for the data. In this review we present the results both from the sponsor's submission as well as this reviewer's findings.

Multiple Comparison/Multiplicity: The protocol had no plan for adjustment for the multiplicity of endpoints.

Analysis Population: Intent-to-treat (ITT) analysis with last observation carried forward (LOCF) was performed. ITT population was defined as: All randomized subjects who took at least one dose of trial medication, and have baseline and one post-baseline assessment for any efficacy parameter (urogenital symptoms, vaginal pH, and Vaginal Maturation Index and Value). This analysis was the primary efficacy analysis. This approach considered subjects in the analysis according to the treatment group to which they were randomized.

3.1.2 Subject Disposition and Demographics

Disposition of Subjects: Of a total of 309 subjects, 306 (99.0%) patients received at least one dose of study drug and had baseline and one post-baseline efficacy evaluation.

Of the 309 patients that were randomized, data was available for 228 subjects at the end of Week-12. Approximately 5% of subjects discontinued the study because of adverse events (placebo: 4.8%, Vagifem 10 µg: 5.4%). Another 5.5% subjects discontinued due to ineffective

therapy (placebo: 10.6%, Vagifem 10 µg: 2.9%). Additionally, 15.4% of subjects in the placebo group and only 8.8% in the Vagifem 10 µg group discontinued because of 'Other' reasons.

Table 1: Subject Disposition

	Placebo n (%)	Vagifem 10 µg n (%)	Total N (%)
No. patients randomized	104	205	309
No. patients completed	70 (67.3)	164 (80.0)	234 (75.7)
No. patients discontinued	34 (32.7)	41 (20.0)	75 (24.3)
Reason for discontinuation			
Adverse event	5 (4.8)	11 (5.4)	16 (5.2)
Protocol non-compliance	2 (1.9)	6 (2.9)	8 (2.6)
Ineffective therapy	11 (10.6)	6 (2.9)	17 (5.5)
Other[a]	16 (15.4)	18 (8.8)	34 (11.0)

Demographics and Baseline Characteristics: The subjects enrolled in this study were, mainly, White (92.9%) and had a mean age of 57.6 years. The demographics and baseline characteristics were comparable across treatment groups. The subjects had a mean BMI value of 25 kg/m2, and were on average 8.1 years from last menses.

Table 2: Subject Demographics and Baseline Characteristics

	Placebo n = 104	Vagifem 10 µg n = 205	Total N = 309
Mean age (SD), years	57.7 (5.27)	57.5 (5.64)	57.6 (5.51)
Range	46 - 75	46 - 81	46 to 81
Race, n (%)			
White	95 (91.3)	192 (93.7)	287 (92.9)
Black or African American	4 (3.8)	6 (2.9)	10 (3.2)
Asian	3 (2.9)	2 (1.0)	5 (1.6)
American Indian or Alaskan Native	0	2 (1.0)	2 (0.6)
Native Hawaiian or Pacific Islander	0	1 (0.5)	1 (0.3)
Other	2 (1.9)	2 (1.0)	4 (1.3)
Body Weight, kg			
Mean (SD)	66.2 (12.0)	66.3 (10.5)	66.2 (11.0)
Range	45.8 – 99.6	40.8 – 95.3	40.8 – 99.6
Body Mass Index, kg/m2			
Mean (SD)	24.9 (4.3)	25.2 (3.5)	25.1 (3.8)
Range	18.0 – 35.0	17.9 – 35.3	17.9 - 35.3
Time since last menses, years			
Mean (SD)	8.2 (5.3)	8.0 (5.8)	8.1 (5.7)
Range	1 - 29	1 - 32	1 – 32
< 2, n (%)	1 (1.0)	2 (1.0)	3 (1.0)
2 to < 5	35 (33.7)	81 (39.5)	116 (37.5)
6 to < 10	33 (31.7)	65 (31.7)	98 (31.7)
≥ 10	35 (33.7)	57 (27.8)	92 (29.8)

Cross-reference: Sponsor's EOT Table 14.1-1 and 14.1-2

3.1.3 Results

Most Bothersome Symptom: Per Division's requirement, the sponsor provided efficacy results based on FDA criteria which includes subjects who met all 3 criteria for vulvar and vaginal atrophy (i.e., moderate to severe most bothersome symptom at baseline, vaginal pH > 5.0, and vaginal superficial cells ≤ 5.0%). This population was defined as modified Intent-to-Treat (mITT) population.

Per protocol, the sponsor's statistical analysis included the use of ANCOVA, provided the normality assumption for using such a method is valid. But there was no indication whether this assumption was verified and the analyses were carried out as if the method was valid. We also performed statistical analysis using the same data sets and the derived outcome data (change from baseline to week 12 LOCF data) included in the data sets. Our statistical method also included ANCOVA, but our analyses were based on ranks because of the violation of the normality assumption.

Table 3 shows the distribution of patients who reported symptoms that were most bothersome to them at baseline and who also met all three criteria. Among the 309 subjects, 122 subjects reported dyspareunia, 58 subjects reported vaginal dryness, and 27 subjects reported vaginal irritation/itching as their most common bothersome symptom at baseline.

Table 3: Mean of Reported Symptoms as Most Bothersome at Baseline (mITT Population)

Symptoms	Vagifem		Placebo	
	n	Mean	n	Mean
Vaginal Dryness (N=58)	36	2.14	22	2.05
Vaginal Irritation/Itching (N=27)	21	2.32	6	2.17
Dyspareunia (N=122)	76	2.62	46	2.63

Table 4 shows the mean change from baseline to week12 for the above most bothersome symptoms. The sponsor's claim that vagifem demonstrated a statistically significant improvement (p=0.015) in dyspareunia over placebo. But our analysis using rank ANCOVA showed an unadjusted p=0.020, and after adjusting for multiplicity we can not conclude that vagifem is statistically superior to placebo in improving the severity of dyspareunia. There were no statistically significant improvements in the change between Vagifem and placebo subjects for the other two MBS symptoms.

Table 4: Mean Change from Baseline to Week 12 by Each Symptoms Reported as Most Bothersome at Baseline, had Vaginal PH>5.0 and Vaginal Superficial Cells ≤ 5.0% (mITT Population, LOCF Analysis)

Symptoms	Vagifem		Placebo		
	n	Mean	n	Mean	P-value *
Vaginal Dryness	36	-1.40	22	-0.91	0.0929
Vaginal Irritation/Itching	21	-1.33	6	-1.00	0.7140
Dyspareunia	76	-1.26	46	-0.89	0.0200

* From ANCOVA on ranks with treatment effect and baseline values as a covariate included in the model.

Table 5 and 6 shows the number of subjects and the mean reported symptoms that are most bothersome moderate-to-severe at baseline and the change from baseline without regard to PH and superficial cells. For dyspareunia, we find 141 subjects who met the above criteria followed by 29 for irritation and 77 for dryness.

Note the average response of severity of the disease at baseline for these subjects were similar to subjects with greater pH level and less superficial cells. The difference between vagifem and placebo treatment in the change from baseline for dyspareunia was smaller and not statistically significantly different.

Overall, these results did not demonstrate adequate and consistent efficacy of vagifem across two analyses population compared to placebo in the treatment of symptoms associated with vaginal atrophy.

Table 5: Mean of Reported Symptoms as Most Bothersome at Baseline (mITT Population)

Symptoms	Vagifem		Placebo	
	n	Mean	n	Mean
Vaginal Dryness (N=58)	52	2.23	25	2.04
Vaginal Irritation/Itching (N=27)	22	2.36	7	2.14
Dyspareunia (N=122)	89	2.64	52	2.65

Table 6: Mean Change from Baseline to Week 12 for Vagifem and Placebo Treated Subjects Who Reported a Moderate to Severe Most Bothersome Symptom at Baseline, Without pH and MI Considerations (mITT Population, LOCF Analysis)

Symptoms	Vagifem		Placebo		
	n	Mean	n	Mean	P-value *
Vaginal Dryness	52	-1.35	25	-0.92	0.2207
Vaginal Irritation/Itching	22	-1.32	7	-1.14	0.8352
Dyspareunia	89	-1.21	52	-0.96	0.1164

* From ANCOVA on ranks with treatment effect and baseline values as a covariate included in the model.

Analysis of Vaginal Maturation Index and Vaginal pH: Based on FDA criteria, the results for vaginal Maturation Index and Vaginal pH at the end of 12 weeks of therapy were statistically significant in favor of Vagifem compared to placebo. There was a significant increase in proportion of superficial cells ($p < 0.001$) and a significant decrease in proportion of vaginal Parabasal cells ($p < 0.001$) for Vagifem subjects compared to placebo subjects. The Vagifem 10 µg group showed a greater number of subjects with normalization of vaginal pH < 5.5 than the placebo group (71.8% vs. 36.3%, respectively). The decreases in the mean Vaginal pH Grade were also significantly greater for Vagifem 10 µg than placebo ($p < 0.001$).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Since theses subjects were all females and similar in age and race, no subgroup analyses were done for these sub-populations.

5. SUMMARY AND CONCLUSIONS

5.1 Conclusions and Recommendations

Based on the data from a single study (VAG-2195), the results do not support the efficacy of Vagifem i (b)(4) Although Vagifem did demonstrate superiority in vaginal pH and maturation index, but it failed to demonstrate statistically significant reductions in the severity of most bothersome symptoms compared to placebo. Based on our analysis using non-parametric method, which is the appropriate analysis method for the submitted data, we do not agree with the sponsor's claim, that vagifem is superior to placebo in (b)(4). The results in subjects meeting criteria of moderate to severe most bothersome symptom at baseline

only, without regard to PH and superficial cells, also demonstrate that Vagifem 10 ug was not statistically significantly superior to placebo in the improvement of vaginal atrophy symptoms.

Therefore, from a statistical perspective, treatment with Vagifem 10 ug did not demonstrate statistically significant improvement in each of the three most bothersome symptoms compared to placebo.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 20-908 / S-013	Submission Dates: 5/26/2009, 7/9/2009, 9/18/2009, 11/12/2009, and 11/18/2009
Brand Name	Vagifem®
Generic Name	Estradiol
Reviewer	Chongwoo Yu, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Novo Nordisk, Inc.
Relevant IND	IND (b)(4)
Submission Type	505(b)(1) – Resubmission: Complete Response (CR)
Formulation; Strength	Vaginal tablets, 10 µg
Indication	(b)(4)

The purpose of this addendum is to address the Clinical Pharmacology related labeling changes that the Sponsor has made according to the Division's recommendations (refer to original Clinical Pharmacology review of NDA 20-908 / S-013, DARRTS, 10/15/2009).

The final agreed upon label between the Sponsor and the Division that was submitted by the Sponsor on November 18, 2009 can be found in Section 1.3. There are no outstanding Clinical Pharmacology issues.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 20-908 / S-013 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Label

14 pages have been removed as (b)(4), draft labeling, immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

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/s/

CHONGWOO YU
11/20/2009

MYONG JIN KIM
11/20/2009

CLINICAL PHARMACOLOGY REVIEW

NDA:	20-908 / S-013
Type/Category:	505(b)(1) - Resubmission: Complete Response (CR)
Brand Name:	Vagifem®
Generic Name:	Estradiol
Relevant INDs:	IND (b)(4)
Indication:	(b)(4)
Dosage Form:	Tablets
Route of Administration:	Vaginal
Dosing Regimen and Strength:	14 days of once daily vaginal insertion of 1 tablet as initial dose and vaginal insertion of 1 tablet twice weekly as maintenance dose, 10 µg
Sponsor:	Novo Nordisk, Inc.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Dates:	May 26, 2009, July 9, 2009, and September 18, 2009
Reviewer:	Chongwoo Yu, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

Vagifem® 10 µg is a lower dose version of the currently marketed, Vagifem® (estradiol [E2] 25 µg vaginal tablet). Vagifem® was approved for the indication of treatment of atrophic vaginitis on March 26, 1999. Initially, it was thought that a dose of E2 25 µg was necessary for the effective treatment of vaginal atrophy.

Vagifem® 10 µg tablets are intended for vaginal administration to postmenopausal women (b)(4). The initial dose is one vaginal tablet daily for two weeks, and the maintenance dose is one vaginal tablet twice a week.

The E2 drug substance and inactive excipients in Vagifem® 10 µg are the same as those in Vagifem® (25 µg). The formulation of Vagifem® 10 µg tablet is identical to Vagifem® (25 µg) except for the reduction of E2 (b)(4).

The Sponsor submitted an efficacy supplement for a lower strength dosage form of Vagifem® that contains 10 µg E2 on December 7, 2007 and additional information including explanation of how the mean change in vaginal pH data for VAG-2195 was measured, recorded, and analyzed was submitted on April 18, 2008. In the same submission, Tables with baseline corrected and uncorrected pharmacokinetics (PK) data for E2, estrone (E1), and estrone sulfate (E1S) with information about how the baseline was derived were submitted as well. The Division issued a Complete Response (CR) letter to the Sponsor on October 15, 2008 due to clinical and statistical deficiencies. Subsequently, the Sponsor submitted their CR resubmission for NDA 20-908 / S-013 to address the deficiencies identified in the Division's CR letter mentioned above. In addition, this submission contains the Sponsor's proposed product labeling. There is no new Clinical Pharmacology or Biopharmaceutics related information submitted other than the proposed product labeling. On July 9, 2009, the Sponsor submitted the Integrated Summary of Safety (ISS) for Studies VAG-2195 and VAG-1748 in Module 5.3.5.3 and the pathology reports for Subject (b)(6) from Study VAG-1748 in Module 1.11.2. The Sponsor has also submitted the revised draft labels and labeling for Vagifem® 10 µg as recommended by Division of Medication Error Prevention and Analysis (DMEPA) on September 18, 2009.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed the Clinical Pharmacology related Sections of the proposed product labeling in this resubmission for NDA 20-908 / S-013 submitted on May 26, 2009, July 9, 2009, and September 18, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

There was no new Clinical Pharmacology or Biopharmaceutics information submitted in this current resubmission. Please refer to the Appendix for labeling recommendations.

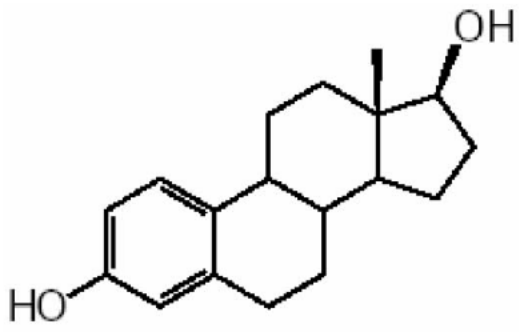
2 QUESTION BASED REVIEW

2.1 General Attributes

Q1. What are the nomenclature, molecular structure, molecular function, and molecular weight of the drug substance?

Chemical name and structure:

17β-estradiol (E2):
Molecular structure:



Empirical formula: $C_{18}H_{24}O_2 \cdot ½H_2O$
Molecular weight: 281.4

Q2. What are the components and composition of the Vagifem® 10 µg final product?

The quantitative composition of each component of the drug product is shown in Table 1below:

Table 1: Quantitative Composition of Each Component of the Drug Product

Name of Ingredients	Quantity mg/tablet [1)]	Function	Reference to standards
Drug substance:			(b)(4)
Estradiol hemihydrate [2)]	10.3 µg [3)]	Active substance	
equivalent to			
estradiol (anhydrous)	10.0 µg		
Other ingredients:	(b)(4)		
Hypromellose			
Lactose monohydrate			
Maize starch [4)]			
Magnesium stearate			
Film-coating: (b)(4)			
Hypromellose (b)(4)			

1) Rounded off figures of three significant figures with a maximum of three decimals are used.
2) Estradiol hemihydrate (b)(4) = Estradiol USP.
3) (b)(4)
4) Maize starch (b)(4)
5) (b)(4)

Q3. How is the Vagifem® 10 µg formulation different from Vagifem® (25 µg)?

The formulation of Vagifem® 10 µg tablet is identical to that of Vagifem® (25 µg) except for the reduction of E2 (b)(4).

The Sponsor is relying on the distribution, metabolism, and excretion profiles of Vagifem® (25 µg).

Q4. What is the proposed mechanism of action?

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, (b)(4) is the principal intracellular human estrogen and is substantially more potent than its metabolites, (b)(4) and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of (b)(4) daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, (b)(4) and the sulfate conjugated form, (b)(4), are the most abundant circulating estrogens in postmenopausal women.

(b)(4)

Q5. What are the proposed indication, dosage, and route of administration?

Vagifem® 10 µg tablets are intended for vaginal administration to postmenopausal women for the (b)(4). The initial dose is one vaginal tablet daily for two weeks, and the maintenance dose is one vaginal tablet twice a week.

2.2 General Clinical Pharmacology and Biopharmaceutics

Q6. What Clinical Pharmacology and Biopharmaceutics related information have been submitted to support this NDA?

This submission contains the following:

- Sponsor's CR to the Division's CR letter issued on October 15, 2008.
- Draft labeling in physician labeling rule (PLR) format

LABELING

The following Clinical Pharmacology related parts of the proposed label were submitted together with this CR for NDA 20-908 / S-013. Strikes are used for deletion and double underline is used for addition in OCP's response to the Sponsor's proposal.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Vagifem safely and effectively. See full prescribing information for Vagifem.

Vagifem® (estradiol vaginal tablets)
Initial U.S. Approval: 1999

WARNING: CARDIOVASCULAR DISORDERS, (b)(4) and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)**
- **Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**

(b)(4).

Estrogen Plua Progestin Therapy

- **Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)**
- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism, and myocardial infarction (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)**
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

----------INDICATIONS AND USAGE----------
Vagifem is an estrogen (b)(4) stradiol) indicated for the treatment of (b)(4) (b)(4) (1)

----------DOSAGE AND ADMINISTRATION----------
Vagifem should be administered intravaginally: (b)(4)

----------DOSAGE FORMS AND STRENGTHS----------

- Vagifem 10 mcg tablet: One vaginal tablet contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of (b)(4). (3)
- Vagifem 25 mcg tablet: One vaginal tablet contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of 1 (b)(4) (3)

----------CONTRAINDICATIONS----------

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active deep vein thrombosis, pulmonary embolism or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction or a history of these conditions (4, 5.2)
- Known liver dysfunction or disease (4, 5.11)
- Known or suspected pregnancy (4, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- The Vagifem applicator may cause vaginal abrasion. (5.17)

- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

----------**ADVERSE REACTIONS**----------
In a prospective, randomized, placebo-controlled, double-blind study the most common adverse reactions ≥5 percent are upper respiratory tract infection, headache, abdominal pain, back pain, genital pruritis, moniliasis, vulvovaginal mycotic infection and diarrhea. (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------*DRUG INTERACTIONS*----------

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism. (7.1)

----------*USE IN SPECIFIC POPULATIONS*----------

- ~~*Nursing Women: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk. (8.3)*~~
- *Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative. (8.5)*

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Patient Labeling.
Revised (b)(4)/2009

Reviewer's comment: *This is not indicated in premenopausal women.*

7 DRUG INTERACTIONS

No (b)(4) drug interaction studies have been conducted for Vagifem.

7.1 Metabolic Interactions

In-vitro and *in-vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects (b)(4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

~~Vagifem should not be used during pregnanc~~ (b)(4) *[see Contraindications (4)]*. ~~There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.~~

Reviewer's comment: *This is not indicated in premenopausal women.*

8.3 Nursing Women

~~Vagifem should not be used during lactatio~~ (b)(4) Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen. ~~Caution should be exercised when Vagifem is administered to a nursing woman.~~

Reviewer's comment: *This is not indicated in premenopausal women.*

8.4 Pediatric Use

Vagifem is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Vagifem to determine whether those over

65 years of age differ from younger subjects in their response to Vagifem (b)(4).

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen-alone substudy (daily conjugated estrogens 0.625 mg versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age *[See Clinical Studies (14.2)]*.
In the WHI estrogen plus progestin substudy, there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater that 65 years of age *[See Clinical Studies (14.2)]*.

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the estrogen-alone and the estrogen plus progestin substudies when compared to placebo *[See Clinical Studies (14.3)]*.

Since both (b)(4) ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [9] *[see Clinical Studies (14.3)]*.

8.6 Renal Impairment

The effect of renal impairment on Vagifem pharmacokinetics has not been studied.

8.7 Hepatic Impairment

(b)(4) The effect of hepatic impairment on Vagifem pharmacokinetics has not

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for Vagifem.

12.3 Pharmacokinetics

Absorption

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

In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Vagifem 10 mcg and 25 mcg demonstrated a mean estradiol (E2) C_{ave} at Day 83 of (b)(4) 5.50 pg/mL for 10 mcg and (b)(4) 11.59 pg/mL, respectively, for 25 mcg after 12 weeks of treatment (b)(4)

(b)(4)

Table 3: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters following Multiple Doses[b] of Vagifem 10 mcg (Uncorrected for baseline, N=29)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/mL)	$C_{ave(0-24)}$ (pg/mL)	%CV[a]	AUC_{0-24} (h.pg/mL)	$C_{ave(0-24)}$ (pg/mL)	%CV[a]	AUC_{0-24} (h.pg/mL)	$C_{ave(0-24)}$ (pg/mL)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Patients received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks.

Table 4: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters following Multiple Doses[b] of Vagifem 25 mcg (Uncorrected for baseline, N[c]=28 or 27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/mL)	$C_{ave(0-24)}$ (pg/mL)	%CV[a]	AUC_{0-24} (h.pg/mL)	$C_{ave(0-24)}$ (pg/mL)	%CV[a]	AUC_{0-24} (h.pg/mL)	$C_{ave(0-24)}$ (pg/mL)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Patients received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks.
[c] N=28 for treatment before Day 14 and N=27 for treatments from Day 14.

Reviewer's comment: *Th* (b)(4) *in the label proposed by the Sponsor will have to be replaced with Tables 3 and 4 that contain PK parameters reported as arithmetic means of all three analytes, E2, E1, and E1S. In addition, the uncorrected PK parameters for baseline should be used instead of corrected parameters for baseline to be consistent with other drugs in the same drug class.*

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and

both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Reviewer's comment: *The Sponsor has adopted information from the current Vagifem® (25 mcg) U.S. Package insert (July, 2003) for Distribution, Metabolism, and Excretion parts of Section 12.3 Pharmacokinetics.*

Use in Specific Populations

Geriatric Use: There have not been sufficient numbers of geriatric women involved in clinical studies utilizing Vagifem to determine whether those over 65 years of age differ from younger subjects in their response to Vagifem.

Renal Impairment: The effect of renal impairment on Vagifem pharmacokinetics has not been studied.

Hepatic Impairment: Vagifem is contraindicated in patients with hepatic impairment. The effect of hepatic impairment on Vagifem pharmacokinetics has not been studied.

Drug Interactions

In-vitro and *in-vivo* studies have shown that estrogens are metabolized partially by CYP3A4. Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort (*Hypericum perforatum*) preparations, phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Reviewer's comment: *Added missing parts into Section 12.3. Vagifem is contraindicated in patients with hepatic impairments.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20908	SUPPL-13	NOVO NORDISK INC	VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHONGWOO YU
10/15/2009

MYONG JIN KIM
10/15/2009

CLINICAL PHARMACOLOGY REVIEW

NDA:	20-908 / S-013
Type/Category:	505(b)(1)
Brand Name:	Vagifem®
Generic Name:	Estradiol 10 µg
Relevant INDs:	IND (b)(4)
Indication:	(b)(4)
Dosage Form:	Tablets
Route of Administration:	Vaginal (local)
Dosing Regimen and Strength:	14 days of once daily vaginal insertion of 1 tablet as initial dose and vaginal insertion of 1 tablet twice weekly as maintenance dose
Sponsor:	Novo Nordisk, Inc.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Dates:	December 7, 2007 (efficacy supplement) April 18, 2008 (additional information)
Reviewer:	Chongwoo Yu, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

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1 EXECUTIVE SUMMARY

The Sponsor has submitted an efficacy supplement for a lower strength dosage form of Vagifem® that contains 10 µg estradiol (E2). Vagifem® 10 µg is a lower dose version of the currently marketed, Vagifem® (E2 25 µg vaginal tablet). Vagifem® was approved for the indication of treatment of atrophic vagintis on March 26, 1999. Initially, it was thought that a dose of E2 25 µg was necessary for the effective treatment of vaginal atrophy. However, according to the Sponsor, the results from existing Vagifem® clinical trials, in which a 10 µg E2 vaginal tablet was included as a comparator for Vagifem® (25 µg E2 tablet), have suggested that the 10 µg E2 tablet was also effective for the relief of the vaginal atrophy symptoms. Furthermore, the Sponsor believes that the long-term safety of the lower dose formulation would be at least comparable and perhaps improved compared to Vagifem® (25 µg) due to the lower E2 systemic absorption.

Vagifem® 10 µg tablets are intended for vaginal administration to postmenopausal women for the (b)(4). The initial dose is one vaginal tablet daily for two weeks, and the maintenance dose is one vaginal tablet twice a week.

The E2 drug substance and inactive excipients in Vagifem® 10 µg are the same as those in Vagifem® (25 µg). The formulation of Vagifem® 10 µg tablet is identical to Vagifem® (25 µg) except for the reduction of E2 (b)(4).

The Sponsor has submitted the results of a bioavailability (BA) clinical trial (VAG-1850) and a pivotal efficacy and safety clinical trial (VAG-2195). In the BA study (VAG-1850), the systemic absorption of E2 from both 10 and 25 µg dose formulations were compared. The Sponsor is proposing to (b)(4) (b)(4) for both 10 and 25 µg from this single dose BA study.

According to the Sponsor, the efficacy of Vagifem® 10 µg in the (b)(4) (b)(4) was established in the pivotal trial, VAG-2195. The 10 µg dose was compared to placebo with respect to the 3 co-primary endpoints: Change from baseline to Week 12 in (1) Vaginal Maturation Index and Maturation Value, (2) Vaginal pH, and (3) the moderate to severe symptom that had been identified by the patient as being most bothersome as recommended in the Division's communication of February 1, 2005, November 15, 2007, and the draft guidance "*Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation*". Study VAG-2195 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial conducted in 308 healthy menopausal women of age 45 years or older across 45 sites in the U.S. and 4 sites in Canada .

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 20-908 submitted on December 7, 2007 and April 18, 2008. The overall Clinical Pharmacology data submitted to support this NDA are acceptable provided that a mutually satisfactory agreement is reached regarding the labeling language.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The E2 drug substance and inactive excipients in Vagifem® 10 µg are the same as those in Vagifem® (25 µg). The formulation of Vagifem® 10 µg tablet is identical to Vagifem® (25 µg) except for the reduction of E2 (b)(4).

Bioavailability of Vagifem® 10 and 25 µg E2 Tablet: Study VAG-1850

A randomized, open label, multiple dose, parallel group, single center BA study was conducted in 58 healthy post-menopausal women with atrophic vaginitis to evaluate the extent of systemic absorption of E2 during treatment with Vagifem® 10 µg and during treatment with Vagifem® (25 µg). Patients received one of the two treatments during the study. Patients received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks. Drug administrations were to take place at a consistent time of the day, preferably in the morning.

Tables 1 and 2 summarizes the plasma E2, estrone (E1), and estrone sulfate (E1S) PK parameters uncorrected for baseline following multiple doses of Vagifem® 10 and 25 µg, respectively.

Table 1: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 2: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Published literature estimates of the normal levels of postmenopausal endogenous E2 fall within the range of 5-25 pg/ml (DeCherney and Nathan, 2003). For the purposes of the Study VAG-1850, a plasma E2 concentration of 20 pg/ml was selected by the Sponsor as a threshold for systemic absorption of clinical interest. Selection of this threshold was based upon the Sponsor's belief that E2 levels below this value definitely fall within the normal range of postmenopausal plasma E2

concentrations, and would therefore not be expected to produce any clinically relevant systemic effects. E2 administered into the vagina at repeated doses of 10 µg was found to display a PK profile that was globally similar in patterns to that following 25 µg administration. Mean plasma concentrations of E2, E1, and E1S were consistently lower for the Vagifem® 10 µg tablet than the currently-marketed Vagifem® (25 µg) formulation. The mean E2 plasma concentration over 24 hr were always below 11 and 21 pg/ml for Vagifem® 10 and 25 µg, respectively, even after 14 days of daily administration. Overall, mean E2 concentration remained within the normal postmenopausal range in both groups, Vagifem® 10 and 25 µg.

Reviewer:
Chongwoo Yu, Ph.D.
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Concurrence:
Myong-Jin Kim, Pharm.D., Team leader
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

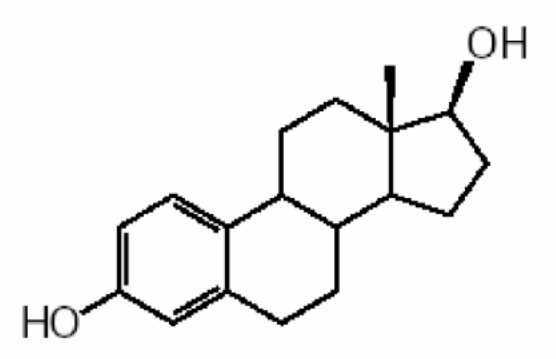
2 QUESTION BASED REVIEW

2.1 General Attributes

Q1. What are the nomenclature, molecular structure, molecular function, and molecular weight of the drug substance?

Chemical name and structure:

17β-estradiol (E2):
Molecular structure:



Empirical formula: $C_{18}H_{24}O_2 \cdot ½H_2O$
Molecular weight: 281.4

Q2. What are the components and composition of the Vagifem® 10 µg final product?

The quantitative composition of each component of the drug product is shown in Table 3 below:

Table 3: Quantitative Composition of Each Component of the Drug Product

Name of Ingredients	Quantity mg/tablet [1]	Function	Reference to standards
Drug substance:			(b)(4)
Estradiol hemihydrate [2]	10.3 µg [3]	Active substance	
equivalent to estradiol (anhydrous)	10.0 µg		
Other ingredients:	(b)(4)		
Hypromellose			
Lactose monohydrate			
Maize starch [4]			
Magnesium stearate			
Film-coating: (b)(4)			
Hypromellose (b)(4)			

1) Rounded off figures of (b)(4) significant figures with a maximum of three decimals are used.
2) Estradiol hemihydrate (b)(4) = Estradio (b)(4)
3) (b)(4) (b)(4)
4) Maize starch (b)(4) = Corn Starch
5) (b)(4)

Q3. How is the Vagifem® 10 µg formulation different from Vagifem® (25 µg)?

The formulation of Vagifem® 10 µg tablet is identical to that of Vagifem® (25 µg) except for the reduction of E2 (b)(4).

The Sponsor is relying on the distribution, metabolism, and excretion profiles of Vagifem® (25 µg).

Q4. What is the proposed mechanism of action?

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, (b)(4) and the sulfate conjugated form, (b)(4) are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

(b)(4)

Vagifem® 10 µg is a local estrogen therapy designed to relieve vaginal symptoms, a major component of the urogenital symptoms found in postmenopausal estrogen deficiency. Vagifem® 10 µg (estradiol viginal tablets) exerts its effect locally in the lower urogenital tract, particularly the vagina, and has not been associated with significant effects in other estrogen-sensitive organ or tissues of the body. Consequently, Vagifem® 10 µg is provides relief of local symptoms of menopause only.

Q5. What are the proposed indication, dosage, and route of administration?

Vagifem® 10 µg tablets are intended for vaginal administration to postmenopausal women for the (b)(4). The initial dose is one vaginal tablet daily for two weeks, and the maintenance dose is one vaginal tablet twice a week.

2.2 General Clinical Pharmacology and Biopharmaceutics

Q6. What Clinical Pharmacology and Biopharmaceutics related information have been submitted to support this NDA?

This submission contains the following:

- Draft labeling in PLR format
- Quality overall summary and information on drug substances and drug products
- BA study report: Multiple Dose PK of Vagifem® 10 and 25 µg E2 Tablet (Study VAG-1850)
- Bioanalytical method validation report
- Clinical summary and study report: Safety/Efficacy of Vagifem® 10 µg Tablet (Study VAG-2195)
- Sponsor's response regarding baseline corrected and uncorrected PK data for E2, E1, and E1S with information about how baseline was derived

Q7. What is the difference between the Vagifem® 10 µg and Vagifem® (25 µg) formulations?

According to the Sponsor, the estradiol drug substance and inactive excipients in Vagifem® 10 µg are almost identical to those in Vagifem® (25 µg) except for the reduction of estradiol (b)(4) (b)(4)

Q8. Is the clinical trial formulation and the to-be-marketed formulation identical?

Yes. The batches used in clinical studies are produced in production size by the same formulation and with the same manufacturing equipment as intended for the to-be-marketed formulation.

Q9. What are the PK parameters of Vagifem® 10 and 25 µg tablets following single dose and multiple dose administration?

A randomized, open label, multiple dose, parallel group, single center BA study was conducted in 58 healthy post-menopausal women with atrophic vaginitis to evaluate the extent of systemic absorption of E2 during treatment with Vagifem® 10 µg or with Vagifem® (25 µg). Patients received one of the two treatments during the study. Every subject received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks. Drug administrations were to take place at a consistent time of the day, preferably in the morning. In-house stays (admission at the study unit) for collection of blood samples and associated plasma concentration testing occurred at Day -2 to -1, Day 1-2, Day 14-15, and Day 82-84. This sample collection schedule allowed determination of plasma concentration profiles for E2, E1, and E1S at the following time points:

- Day -1 (baseline profile, starting 24 hr before first dosing): 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr,
- Days 1-2: 0 (pre-dose - corresponding to Day -1, 24 hr), 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr post administration (p.a.)
- Days 14-15: 0 (pre-dose), 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr p.a.
- Days 82-83 (baseline profile, starting 24 hr before dosing on Day 83): 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr
- Days 83-84: 0 (pre-dose – corresponding to Day 82, 24 hr): 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr p.a.

- Days 7, 30, and 58 (trough values): 0 (pre-dose)

A total of 63 blood samples were drawn during the study for drug analysis. Plasma was prepared and stored at or below -20 ºC until analysis.

Tables 4 and 5 summarize the plasma E2, E1, and E1S PK parameters uncorrected for baseline following multiple doses of Vagifem® 10 and 25 µg, respectively. Please note that Day 1 data represents the single dose PK parameters of Vagifem® 10 and 25 µg.

Table 4: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Uncorrected, N=27)

	E2			.E1			E1S		
	AUC_{0-24} (pg.h/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 5: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (pg.h/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Published literature estimates of the normal levels of postmenopausal endogenous E2 fall within the range of 5-25 pg/ml (DeCherney and Nathan, 2003). For the purposes of the Study VAG-1850, a plasma E2 concentration of 20 pg/ml was selected by the Sponsor as a threshold for systemic absorption of clinical interest. Selection of this threshold was based upon the Sponsor's belief that E2 levels below this value definitely fall within the normal range of postmenopausal plasma E2 concentrations, and would therefore not be expected to produce any clinically relevant systemic effects. Mean plasma concentrations of E2, E1, and E1S were consistently lower for the Vagifem® 10 µg tablet than the currently-marketed Vagifem® (25 µg) formulation. All of the subjects receiving the Vagifem® 10 µg formulation had average plasma E2 concentrations below 20 pg/ml at all assessment days. In contrast, in the Vagifem® (25 µg) tablet group, the proportion of subjects having average plasma E2 concentrations of 20 pg/ml or more was 54% at Day 1, 37% at Day 14, and 15% at Day 83. However, for both doses mean E2 $C_{ave(0-24)}$ remained below 21 pg/ml at each testing day. Both treatments were safe and well tolerated. No serious adverse events (SAE) were reported and none of the subjects withdrew due to an adverse event (AE).

Q9. Were the PK data submitted from the Sponsor corrected or uncorrected for the baseline? If it was corrected for the baseline, how was the baseline derived?

The PK data submitted in the study report VAG-1850 are uncorrected for baseline and were reported as geometric means. Per the Division's request, the Sponsor also submitted PK data for both uncorrected and corrected for baseline reported as arithmetic means. The baseline was derived by a full 24 hr PK profile performed at baseline on Day -1, (Day -1 baseline profile, starting 24 hr before first dosing at 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr). Detail baseline information can be found on pages 20, 23, and 27 of this review.

Q10. Is the new Vagifem® (25 µg) PK data obtained from Study VAG-1850 comparable to the PK data on the current Vagifem® label?

PK data from Study VAG-1850 show lower E2, and E1 levels but a similar PK curve pattern compared to the current label throughout the study. This might be explained by the difference in analytical techniques employed in studies. It was noted that a radio immunoassay was used in Study 10/USA and mass spectrometry based assays (i.e., GC-MS, LC-MS/MS) were used in Study VAG-1850. Table 6 summarizes arithmetic AUC_{0-24} means of E2, E1, and E1S from the Current Label (Study 10/USA) and the new data submitted (Study VAG-1850) for Vagifem® (25 µg).

Table 6: Comparison of Arithmetic AUC_{0-24} Means of E2, E1, and E1S from the Current Label (Study 10/USA) vs. New Data Submitted (Study VAG-1850) for Vagifem® (25 µg)

AUC_{0-24} (pg·h/ml)	25 µg / E2		25 µg / E1		10 µg / E2		10 µg / E1	
	10/USA	VAG-1850	10/USA	VAG-1850	10/USA	VAG-1850	10/USA	VAG-1850
Day 1	538	495.27	649	567.07	349	242.08	519	485.21
Day 14	567	466.63	744	662.94	255	176.49	558	496.14
Day 83	563	278.27	681	500.06	264	132.04	568	411.08

Q11. Did the Sponsor use validated bioanalytical assays to generate the study data?

Yes. In Study VAG-1850, a gas chromatography - mass spectrometry (GC-MS) assay was used to measure E2 and E1 and a liquid chromatography - tandem mass spectrometry (LC-MS/MS) assay was used to measure E1S as necessary. These assays were validated and have successfully met the acceptance criteria including accuracy and precision as outlined in the FDA Guidance to Industry entitled "Bioanalytical Method Validation". Detail assay validation information can be found on pages 14-16 in this review.

The concentration ranges of the E2, E1, and E1S calibration curves were 2.5-125 pg/ml, 5-250 pg/ml, and 50-5000 pg/ml, respectively.

During the study, the mean coefficient of determination (r^2) was 0.999 for E2 and E1 and 0.996 for E1S. The linearity of the analytical methods have been demonstrated successfully.

A total of (b)(4) plasma samples for E2, E1, and E1S were transferred from the Clinical Division of (b)(4) to the Analytical Division in several groups between February 6, 2007 and May 14, 2007. Samples were stored at -20 ºC prior to sample analysis.

LABELING

The following Clinical Pharmacology related parts of the proposed label were submitted together with this efficacy supplement NDA. Strikes are used for deletion and double underline is used for addition in OCP's response to the Sponsor's proposal.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Vagifem safely and effectively. See full prescribing information for Vagifem.

Vagifem® (estradiol vaginal tablets)
Initial U.S. Approval: 1999

(b)(4)

----------INDICATIONS AND USAGE----------
Vagifem is an estrogen indicated in the (b)(4). (1)

----------DOSAGE AND ADMINISTRATION----------
Vagifem should be administered vaginally. (b)(4)

- (b)(4)
-

----------DOSAGE FORMS AND STRENGTHS----------

- Vagifem 10 mcg tablet: One vaginal tablet contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol. (3)
- Vagifem 25 mcg tablet: One vaginal tablet contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol. (3)

----------CONTRAINDICATIONS----------

- Undiagnosed abnormal genital bleeding. (4)
- (b)(4)
-
-
-
- Known liver dysfunction or disease. (4, 5.11)
- Known or suspected pregnancy. (4, 8.1)
- (b)(4)

----------WARNINGS AND PRECAUTIONS----------

(b)(4)

- Estrogens increase the risk of gallbladder disease (b)(4)
- Discontinue estrogens if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs. (5.5, 5.6, 5.10, 5.11)
- (b)(4)
- Monitor thyroid function in patients on thyroid replacement therapy. (5.12 (b)(4)

----------ADVERSE REACTIONS----------
Most common adverse reactions are (incidence ≥5%) upper respiratory tract infection, headache, abdominal pain, back pain, pruritis genital, and moniliasis (b)(4), vulvovaginal mycotic infection and diarrhea. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------*DRUG INTERACTIONS*----------

(b)(4)

----------*USE IN SPECIFIC POPULATIONS*----------

- ***Nursing Mothers: Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. (8.3)***
- ***Geriatric Use: An increased risk of probable dementia in women over (b)(4) years of age was reported in the (b)(4) Initiative Memory Study. (8.5)***

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

7 DRUG INTERACTIONS

No (b)(4) drug interaction studies have been done for Vagifem.

7.1 Metabolic Interactions

In-vitro and in-vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.3 Pharmacokinetics

Absorption

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

In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Vagifem 10 mcg and 25 mcg demonstrated a mean estradiol (E2) C_{ave} at Day 83 of (b)(4) pg/mL for 10 mcg an (b)(4) pg/mL for 25 mcg after 12 weeks of treatment.
(see Table 3)

(b)(4)

Table 3: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Uncorrected, (b)(4))

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 4: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Uncorrected, (b)(4))

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495 27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278 27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

(b)(4)

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Comments

- The Sponsor has incorporated the multiple dose PK data of Vagifem® 10 and 25 µg in the *Absorption* part of Section 12.3 Pharmacokinetics. The Sponsor has adopted information from the current Vagifem® (25 µg) U.S. Package insert (July, 2003) for *Distribution, Metabolism,* and *Excretion* parts of Section 12.3 Pharmacokinetics.
- The (b)(4) in the label proposed by the Sponsor will have to be replaced with a table that contains PK parameters reported as arithmetic means of all three analytes, E2, E1, and E1S.

Appendix

A.1. Individual Study Review

A.1.1. BA Study: VAG-1850

A Pharmacokinetic Randomized Study with a Parallel Group Design to Assess the Extent of Systemic Absorption of Estradiol During Treatment with a 10 µg or 25 µg Estradiol Vaginal Tablet Administered Once Daily for 2 Weeks followed by 10 Weeks of Twice-Weekly Maintenance Therapy in Postmenopausal Women with Atrophic Vaginitis

Protocol No:	VAG-1850
Phase:	1
Principal Investigator:	(b)(4)
Clinical Study Center:	
Clinical Study Dates:	
Analytical Study Facility:	
Analytical Study Dates:	February 13, 2007 - June 27, 2007

OBJECTIVE

The primary objective of the study was to evaluate the extent of systemic absorption of E2 during treatment with Vagifem® 10 and 25 µg in postmenopausal women with atrophic vaginitis. Safety (i.e., Adverse event incidence during the whole study, vital signs, ECG, physical examination, and laboratory investigations during screening and end-of-trial visit) was evaluated as a secondary endpoint.

STUDY DESIGN, TREATMENT, AND SUBJECTS

A randomized, open label, multiple dose, parallel group, single center BA study was conducted in 58 healthy post-menopausal women with atrophic vaginitis to evaluate the extent of systemic absorption of E2 during treatment with Vagifem® 10 µg or Vagifem® (25 µg). All subjects were Caucasian females. Subjects ranged in age from 60 to 70 years (mean 65.2, SD 2.9.), with serum baseline E2 levels < 20 pg/ml, FSH> 40 mIU/ml. The mean height was 160 cm (range of 150-180 cm, SD 10), the mean weight was 65.4 kg (range of 47.6-97 kg, SD 9.7), and the mean body mass index (BMI) was 24.8 kg/m^2 (range of 18.5-30 kg/m^2, SD 3.1). Inclusion criteria included vaginal cytology with 5% superficial cells, and vaginal pH ≥ 5. Subjects had not used estrogen/progestin hormone replacement therapy (oral, transdermal, spray, vaginal preparation//implants) within 3 months prior to first trial drug administration, or replacement hormone injections within 6 months prior to first trial drug administration.

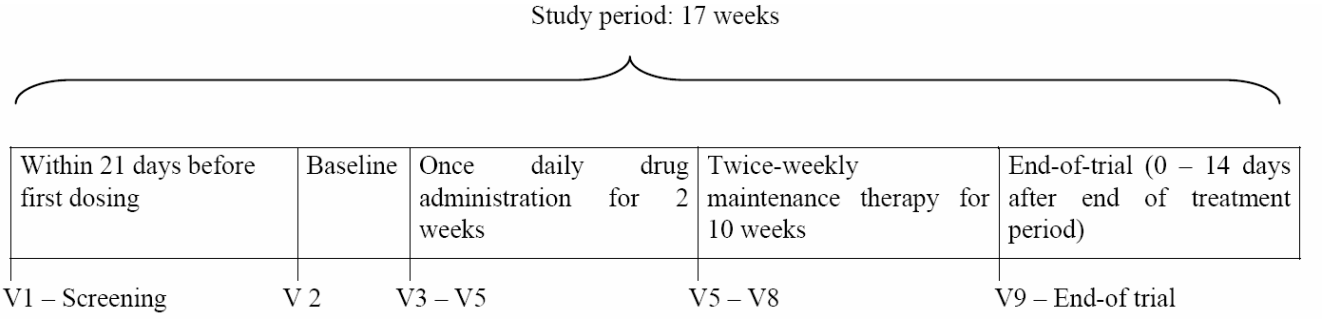
Subjects were screened 3 weeks prior to the treatment start. A total of 9 visits for subjects completing the trial were planned as follows:

Visit 1 (Screening)	
Visit 2 (Baseline, Day -2 to -1) + Visit 3 (First dosing, Day 1-2):	appointment within 21 days after Visit 1; admission to study unit on the evening of Day -2; in-house with 3 overnight stays
Visit 4 (Day 7)	ambulatory appointment, 6 days (± 1 day) after first drug administration
Visit 5 (Day 14-15):	in-house with 1 overnight stay, 13 days (± 1 day) after first drug administration
Visit 6 (Day 30):	ambulatory appointment, 29 days (± 1 day) after first drug administration
Visit 7 (Day 58):	ambulatory appointment, 57 days (± 1 day) after first drug administration
Visit 8 (Day 82-84):	in-house with 2 overnight stays, 81 days (± 1 day) after first drug administration
Visit 9 (End-of-trial):	0 – 14 days (+1 day) after end of treatment period

Subjects were randomized in a 1:1 ratio to receive one of the two treatments during the study. Every subject received vaginal tablets as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks. Drug administrations were to take place at a consistent time of the day, preferably in the morning. Study treatments were designed as AB or CD by the following definitions:

- Group AB: 14 days of once-daily administration of Vagifem® 10 µg followed by 10 weeks of twice-weekly administration of Vagifem® 10 µg

- Group CD: 14 days of once-daily administration of Vagifem® 25 µg followed by 10 weeks of twice-weekly administration of Vagifem® 25 µg



PHARMACOKINETIC EVALUATION

Blood sampling

In-house stays (admission at the study unit) for collection of blood samples and associated plasma concentration testing occurred at Day -2 to -1, Day 1-2, Day 14-15, and Day 82-84. This sample collection schedule allowed determination of plasma concentration profiles for E2, E1, and E1S at the following time points:

- Day -1 (baseline profile, starting 24 hr before first dosing): 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr,
- Days 1-2: 0 (pre-dose - corresponding to Day -1, 24 hr), 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr post administration (p.a.)
- Days 14-15: 0 (pre-dose), 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr p.a.
- Days 82-83 (baseline profile, starting 24 hr before dosing on Day 83): 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr
- Days 83-84: 0 (pre-dose – corresponding to Day 82, 24 hr): 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr p.a.
- Days 7, 30, and 58 (trough values): 0 (pre-dose)

A total of 63 blood samples were drawn during the study for drug analysis. Plasma was prepared and stored at or below -20 ºC until analysis.

Analytical method

A GC-MS assay was used to measure E2 and E1 and a LC-MS/MS assay was used to measure E1S as necessary. These assays were validated and have successfully met the acceptance criteria outlined in the FDA Guidance to Industry entitled “Bioanalytical Method Validation”.

	E2	E1	E1S
Concentration Range	2.5-125 pg/ml	5.0-250 pg/ml	50-5000 pg/ml
LLOQ	2.5 pg/ml	5.0 pg/ml	50 pg/ml

Table 7: Overall Back-calculated E2 Standard Concentrations from Calibration Curves

Cal. std. nominal conc. [pg/mL]	**2.50**	**6.25**	**12.5**	**25.0**	**50.0**	**75.0**	**113**	**125**
Number	57	55	57	55	57	57	57	57
Mean (calc.)	2.53	6.25	12.4	24.9	50.2	74.9	113	124
sd	0.126	0.220	0.407	0.677	1.45	1.55	2.41	2.16
cv (%)	5.00	3.52	3.29	2.72	2.88	2.07	2.13	1.74
Bias (%)	1.01	-0.06	-0.95	-0.41	0.41	-0.17	0.65	-0.49

Table 8: Overall Back-calculated E1 Standard Concentrations from Calibration Curves

Cal. std. nominal conc. [pg/mL]	**5.00**	**12.5**	**25.0**	**50.0**	**100**	**150**	**225**	**250**
Number	57	57	56	56	57	57	57	57
Mean (calc.)	4.99	12.5	25.1	49.8	100	150	225	249
sd	0.231	0.580	0.902	1.38	2.39	3.55	4.62	4.37
cv (%)	4.63	4.65	3.59	2.78	2.38	2.37	2.05	1.75
bias (%)	-0.18	-0.14	0.32	-0.36	0.50	-0.04	0.20	-0.31

Table 9: Overall Back-calculated E1S Standard Concentrations from Calibration Curves

Cal. std. nominal conc. [pg/mL]	**50.0**	**100**	**200**	**500**	**1000**	**2000**	**4500**	**5000**
Number	58	58	58	59	58	59	59	59
Mean (calc.)	49.7	99.2	202	502	992	2020	4560	4920
sd	4.61	6.97	12.4	29.6	77.7	117	268	250
cv (%)	9.29	7.03	6.13	5.91	7.83	5.78	5.88	5.07
bias (%)	-0.64	-0.85	0.97	0.39	-0.81	1.15	1.30	-1.53

During the study, the mean coefficient of determination (r^2) was 0.999 for E2 and E1 and 0.996 for E1S. The linearity of the analytical methods has been demonstrated successfully.

A total of (b)(4) plasma samples for E2, E1, and E1S were transferred from the Clinical Division of (b)(4) to the Analytical Division in several groups between February 6, 2007 and May 14, 2007. Samples were stored at -20 ºC prior to sample analysis.

For E2, the concentration range was 2.5-125 pg/ml, with a LLOQ of 2.5 pg/ml. Quality Control (QC) samples of 2.5, 7.5, 37.5,, and 100 pg/ml were analyzed with each run and had mean CVs less than or equal to 9.16%.

For E1, the concentration range was 5-250 pg/ml, with a LLOQ of 5 pg/ml. QC samples of 5, 15, 75, and 200 pg/ml were analyzed with each run and had mean CVs less than or equal to 5.93%.

For E1S, the concentration range was 50-5000 pg/ml, with a LLOQ of 50 pg/ml. QC samples of 150, 400, and 4000 pg/ml were analyzed with each run and had mean CVs less than or equal to 8.74%.

DATA ANALYSIS

Pharmacokinetic Analysis

Primary and secondary parameters were determined on Days -1, 1-2 (single dose), 14-15, 82-83, and 83-84 (steady state) from plasma concentration-time data using the actual times of sample collection.

- Primary parameter: AUC_{0-24} of E2
- Secondary parameters: AUC_{0-24} of E1 and E1S, $C_{ave(0-24)}$, C_{max}, C_{min}, and T_{max} of E2, E1, and E1S

Statistical Analysis

PK parameters were calculated by non-compartmental methods, e.g., linear trapezoidal rule for AUC. There were no statistical hypotheses to be formally tested, all evaluations being purely exploratory. AUC_{0-24}, $C_{ave(0-24)}$ for E2, E1, and E1S were compared for each treatment separately, with AUC_{0-24} for E2 considered to be the primary endpoint. These profiles were obtained for Day -1 (baseline profile before treatment), Day 1-2 (after first drug administration), Day 14-15 (end of drug administration once daily), Day 82-83 (prior to last drug administration during the stage of twice-weekly maintenance therapy), and Day 83-84 (after last drug administration). Pair-wise comparisons between time points (within treatment group) were performed after logarithmic transformation utilizing the paired t-test, and mean differences (between time points) with corresponding 95% confidence intervals and associated p-values were calculated (without adjustment for multiplicity due to the exploratory nature of the analysis). For E2 only, the 20 pg/ml threshold was chosen as the E2 level that remains in the published postmenopausal range. Hence, the percentage of subjects (by time point and treatment) for whom $C_{ave(0-24)}$ of E2 remains below 20 pg/ml was also given.

Safety Evaluations and Adverse Events

Safety evaluation included vital signs, physical exam, ECG, laboratory tests, and adverse events (AE) monitoring. No serious adverse events were reported during the study and no subjects were withdrawn from the therapy due to an adverse event. In this trial, the most common AEs (≥ 5% of subjects) were headache, nausea, nasopharyngitis, vaginal discharge, diarrhea, peripheral edema, weight increased, pharyngolaryngeal pain, back pain, metrorrhagia, vomiting, pain in extremity, haematoma, hot flash, phlebitis, flatulence, cough, fall, bronchitis, dizziness, and malaise. Two subjects were withdrawn from the study (both from Group CD), due to an increased Gamma-GT (GGT) before first dosing or non-compliance during early treatment period.

PHARMACOKINETIC RESULTS

The PK data submitted in the study report VAG-1850 are uncorrected for baseline and were reported as geometric means.

Estradiol (E2)

Group AB (Vagifem 10 µg, Refer to Figure 1 and Table 10)

- Day -1: mean systemic E2 values were essentially constant over the 24 hr period remaining at approximately 3-4 pg/ml
- Day 1: mean $C_{ave(0-24)}$ was 9.39 pg/ml and mean C_{max} was 26.17 pg/ml. The mean concentration had almost returned to baseline by 24 hr.
- Day 14: the mean E2 curve had returned to the constant pattern observed at Day -1, with a mean C_{ave} of 6.56 pg/ml, however, a doubling of mean AUC_{0-24} and mean C_{max} compared to Day -1, the latter being 10.9 pg/ml
- Day 82: following 10 weeks of twice weekly administration, the mean C_{ave} was 1.87 pg/ml and the mean E2 plasma concentration was slightly lower than baseline for the entire 24 hr period and a decrease in mean AUC_{0-24} was observed.
- Day 83: the last administration, plasma concentration rose to a mean C_{max} of 9.99 pg/ml and stabilized after 8 hr at approximately the same concentration as Day 14.

Group CD (Vagifem 25 µg, Refer to Figure 2 and Table 10)

- Day -1 and 1: similar pattern to Vagifem 10 µg with a higher mean C_{max} at Day 1.
- Day 14: constant mean C_{ave} below 20 pg/ml with a C_{max} of 33.65 pg/ml,
- Day 82: similar pattern to the Vagifem 10 µg group with a constant mean C_{ave} slightly lower than baseline.
- Day 83: a higher mean C_{max} of 18.57 pg/ml observed.

It was noted that there was a very high degree of variability observed for Group AB at baseline (geometric CV: 97.4%) with mean AUC_{0-24} being 28% higher in Group CD but mean C_{max} being only 5% higher. The largest difference between Groups AB and CD was the mean C_{ave} on Day 14 that were 6.56 and 18.29, respectively.

Figure 1: Mean Concentration Profile of E2 in Plasma at All Days in Group AB (Vagifem® 10 µg)

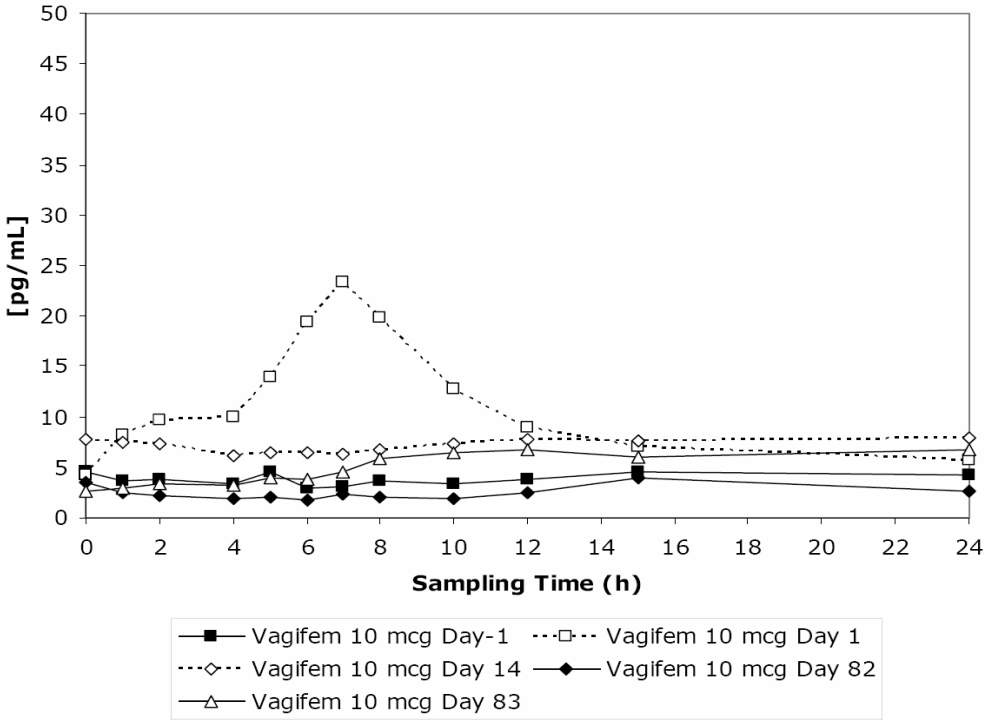


Figure 2: Mean Concentration Profile of E2 in Plasma at All Days in Group CD (Vagifem® 25 µg)

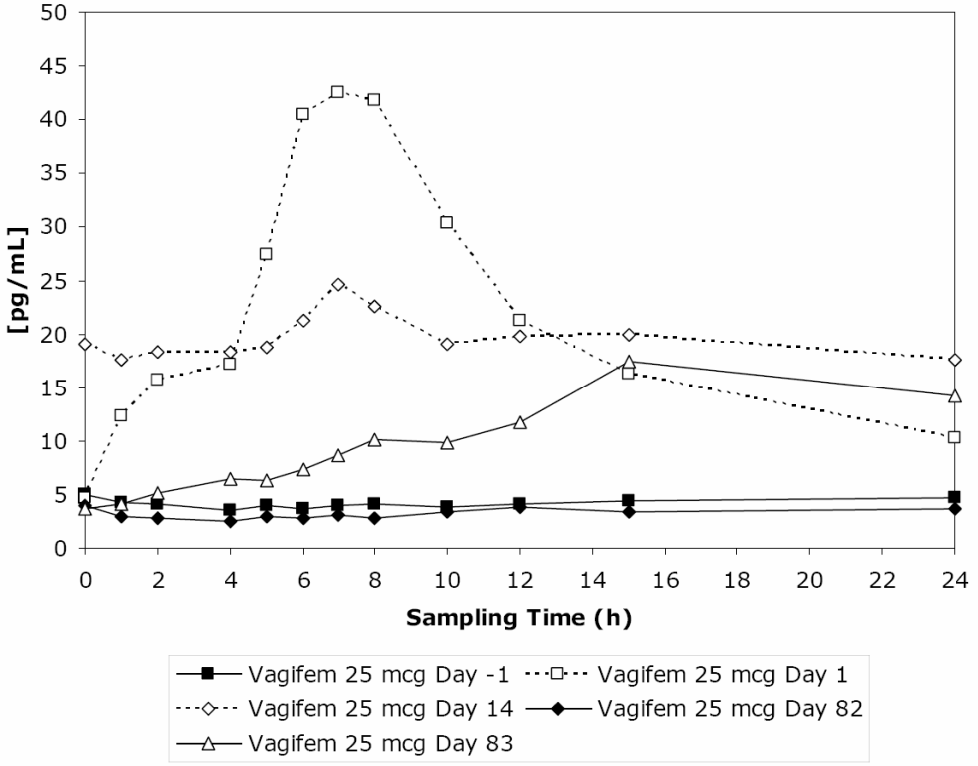


Table 10: Overall Geometric Mean (% CV) PK parameters from Plasma E2 Concentrations

Vagifem® 10 µg (Group AB), N=29					
	AUC_{0-24} (pg h/ml)	$C_{ave(0-24)}$ (pg/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	T_{max} (pg/ml)
Day -1	75.65 (97.4)	3.15 (97.4)	5.59 (67.9)	3.98 (40.4)	12.0
Day 1	225.35 (45.2)	9.39 (45.2)	26.17 (66.1)	4.54 (39.7)	8.0
Day 14	157.47 (57.0)	6.56 (57.0)	10.91 (57.7)	4.78 (33.3)	10.0
Day 82	44.95 (160.5)	1.87 (160.5)	5.07 (64.3)	3.39 (29.6)	5.0
Day 83	111.41 (84.6)	4.64 (84.6)	9.99 (74.2)	3.35 (32.4)	12.0
Vagifem® (25 µg) (Group CD), N[a]=28 or 27					
	AUC_{0-24} (pg h/ml)	$C_{ave(0-24)}$ (pg/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	T_{max} (pg/ml)
Day -1	96.66 (51.2)	4.03 (51.2)	5.89 (33.7)	3.49 (26.0)	10.0
Day 1	476.14 (31.3)	19.84 (31.3)	58.06 (57.4)	4.48 (33.1)	8.0
Day 14	438.87 (39.1)	18.29 (39.1)	33.65 (56.0)	9.02 (53.1)	8.0
Day 82	48.13 (208.1)	2.01 (208.1)	5.29 (46.1)	3.74 (38.9)	7.5
Day 83	225.94 (77.7)	9.41 (77.7)	18.57 (98.0)	4.26 (39.5)	15.0

[a] N=28 for treatments before Day 14 and N=27 for treatments from Day 14

Per the Division's request, the Sponsor has submitted PK data for both uncorrected and corrected for baseline reported as arithmetic means. The baseline was derived by a full 24 hr PK profile performed at baseline on Day -1, (Day -1 baseline profile, starting 24 hr before first dosing at 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr). Tables 11-14 provide an overview of the data submitted. Tables 15 and 16 show how the baseline was derived for Vagifem® 10 µg and 25 µg, respectively.

Table 11: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 12: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Corrected, N=27)

	E2			E1			E1S		
	AUC_{0-24}[b] (h.pg/ml)	$C_{ave(0-24)}$[c] (pg/ml)	%CV[a]	AUC_{0-24}[d] (h.pg/ml)	$C_{ave(0-24)}$[e] (pg/ml)	%CV[a]	AUC_{0-24}[f] (h.pg/ml)	$C_{ave(0-24)}$[g] (pg/ml)	%CV[a]
Day 1	146.66	6.11	50.65	66.99	2.79	124.94	1321.82	55.08	112.07
Day 14	81.06	3.38	98.56	77.91	3.25	129.20	2486.90	103.62	75.14
Day 83	36.61	1.53	209.81	-7.14	-0.30	-1232.56	-31.86	-1.33	-3536.09

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Baseline = 95.43, [c] Baseline = 3.98, [d] Baseline = 418.22, [e] Baseline = 17.43, [f] Baseline = 3836.51, [g] Baseline = 159.85

Table 13: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 14: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Corrected, N=27)

	E2			E1			E1S		
	AUC_{0-24}[b] (h.pg/ml)	$C_{ave(0-24)}$[c] (pg/ml)	%CV[a]	AUC_{0-24}[d] (h.pg/ml)	$C_{ave(0-24)}$[e] (pg/ml)	%CV[a]	AUC_{0-24}[f] (h.pg/ml)	$C_{ave(0-24)}$[g] (pg/ml)	%CV[a]
Day 1	393.72	16.41	32.13	116.16	4.84	60.27	2461.94	102.58	51.11
Day 14	365.78	15.24	42.18	208.40	8.68	46.23	4451.09	185.46	54.00
Day 83	177.42	7.39	93.26	45.52	1.90	270.00	836.03	34.86	157.37

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Baseline = 101.55, [c] Baseline = 4.23, [d] Baseline = 450.92, [e] Baseline = 18.79, [f] Baseline = 3276.38, [g] Baseline = 136.52

Table 15: Summary of E2 Baseline Derived for Vagifem® 10 µg

Variable	(b)(4)	N	Minimum	Median	Maximum	Mean	Std Dev	Coeff of Variation
AUCbase		29	0.00	88.95	307.09	95.43	69.43	72.76
CAVbase		29	0.00	3.71	12.80	3.98	2.89	72.76
AUC24		29	44.60	246.66	398.58	242.08	79.95	33.02
AUC24_d		29	-25.41	150.60	275.30	146.66	74.28	50.65
CAV		29	1.86	10.28	16.61	10.09	3.33	33.02
CAV_d		29	-1.06	6.28	11.47	6.11	3.09	50.65

Table 16: Summary of E2 Baseline Derived for Vagifem® (25 µg)

Variable	(b)(4)	N	Minimum	Median	Maximum	Mean	Std Dev	Coeff of Variation
AUCbase		28	0.00	98.61	202.59	101.55	43.14	42.49
CAVbase		28	0.00	4.11	8.44	4.23	1.80	42.49
AUC24		28	170.43	485.24	671.59	495.27	127.31	25.70
AUC24_d		28	60.08	392.46	645.42	393.72	126.52	32.13
CAV		28	7.10	20.22	27.98	20.64	5.30	25.70
CAV_d		28	2.50	16.35	26.89	16.41	5.27	32.13

Estrone (E1)

Group AB (Vagifem 10 µg, Refer to Figure 3 and Table 17)

- Day -1: the concentration-time curve follows a pattern of initial slight decrease in mean plasma concentration from 20-25 pg/ml followed by a slight increase from 12 hr, returning to the T0 levels
- Day 1: mean C_{max} was 23.64 pg/ml at approximately 8 hrs post-dose with a subsequent decrease of mean systemic concentrations to 12 hr and then increase to 24 hr. Overall, concentrations are higher at Day 1 than at baseline.
- Day 14: similar evolution was observed as Day 1 with T_{max} occurring at 24 hr (mean C_{max} of 26.86 pg/ml)
- Day 82 and 83: the plasma E1 concentrations displayed a similar pattern and levels as at baseline

Group CD (Vagifem 25 µg, Refer to Figure 4 and Table 17)

- The pattern and evolution at subsequent time points of the mean time-concentration curves were generally similar to the Vagifem 10 µg group
- Day 14: AUC_{0-24} and C_{max} were 54% and 46% higher than at Day -1, respectively
- Day 83: AUC_{0-24} and C_{max} were 11-12% higher than baseline

The inter-subject variability of PK parameters was moderate to high in both groups, with geometric CV typically ranging from 24-63%. The largest difference between groups for C_{max} was observed at Day 1, with the 25 µg group being 34% higher. For AUC_{0-24}, the largest difference, 36% was observed at Day 14. At Day 82 and 83, Group CD was 17-23% higher for AUC_{0-24} and C_{max}.

Figure 3: Mean Concentration Profile of E1 in Plasma at All Days in Group AB (Vagifem® 10 µg)

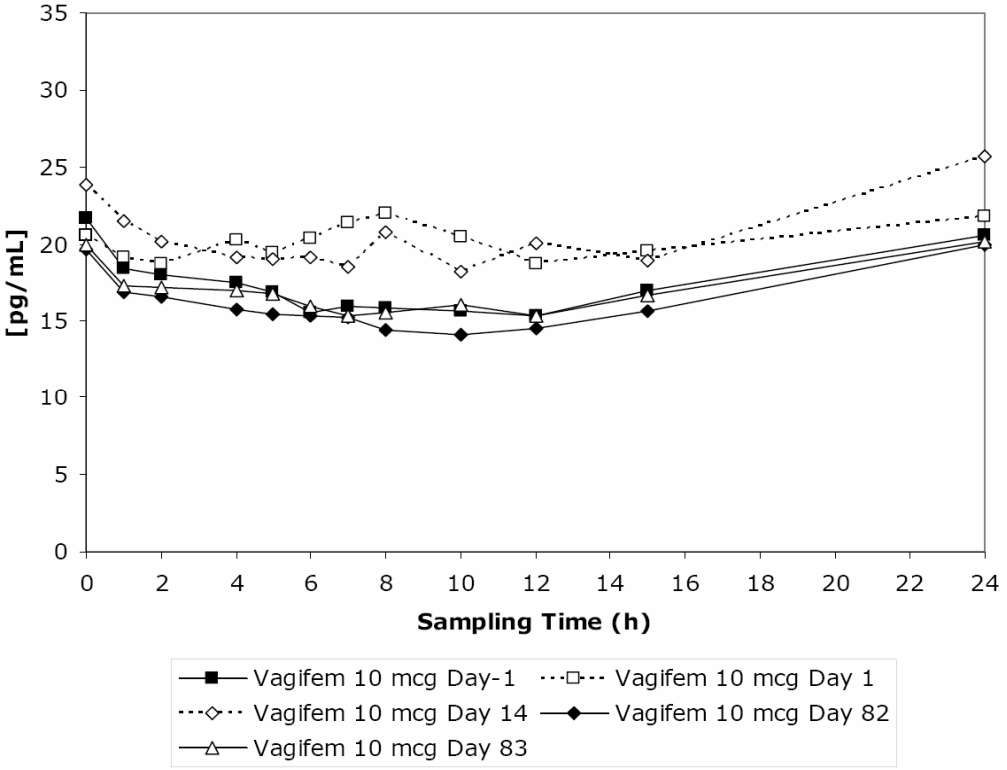


Figure 4: Mean Concentration Profile of E1 in Plasma at All Days in Group CD (Vagifem® 25 µg)

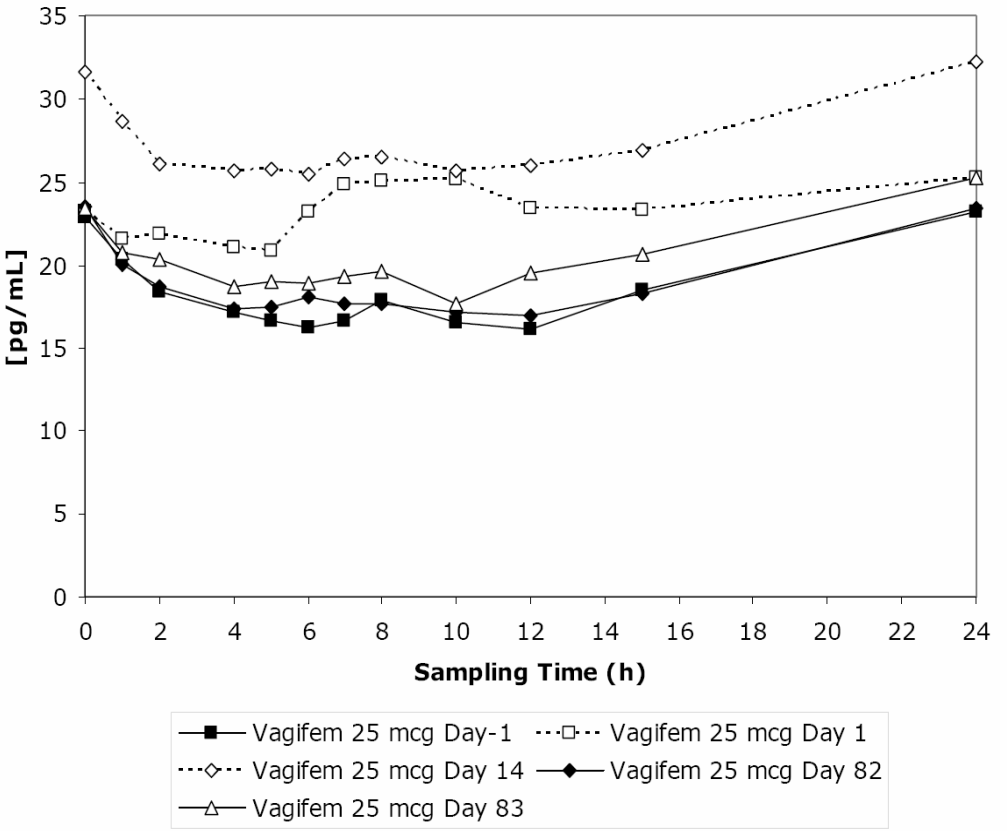


Table 17: Overall Geometric Mean (% CV) PK parameters from Plasma E1 Concentrations

Vagifem® 10 µg (Group AB), N=29					
	AUC_{0-24} (pg h/ml)	$C_{ave(0-24)}$ (pg/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	T_{max} (pg/ml)
Day -1	371.41 (62.5)	15.48 (62.5)	21.54 (45.2)	13.01 (42.9)	0
Day 1	445.91 (43.9)	18.58 (43.9)	23.64 (46.3)	15.20 (37.7)	7
Day 14	473.39 (32.4)	19.72 (32.4)	26.86 (40.0)	15.42 (37.0)	24
Day 82	363.34 (41.2)	15.14 (41.2)	20.57 (35.3)	11.76 (44.8)	8
Day 83	382.28 (40.5)	15.93 (40.5)	22.02 (37.1)	12.38 (40.7)	5
Vagifem® (25 µg) (Group CD), N[a]=28 or 27					
	AUC_{0-24} (pg h/ml)	$C_{ave(0-24)}$ (pg/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	T_{max} (pg/ml)
Day -1	422.42 (39.8)	17.60 (39.8)	23.92 (38.1)	14.38 (36.0)	1.5
Day 1	544.49 (29.9)	22.69 (29.9)	31.68 (30.8)	16.79 (39.4)	8
Day 14	644.55 (24.6)	26.86 (24.6)	34.99 (24.8)	21.00 (28.9)	7
Day 82	425.21 (43.6)	17.72 (43.6)	24.42 (40.5)	13.98 (46.3)	0
Day 83	468.56 (39.7)	19.52 (39.7)	26.87 (36.0)	15.03 (39.6)	24

[a] N=28 for treatments before Day 14 and N=27 for treatments from Day 14

Per the Division's request, the Sponsor has also submitted PK data for both uncorrected and corrected for baseline reported as arithmetic means. The baseline was derived by a full 24 hr PK profile performed at baseline on Day -1, (Day -1 baseline profile, starting 24 hr before first dosing at 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 15, and 24 hr). Tables 18-21 provide an overview of the data submitted. Tables 22 and 23 show how the baseline was derived for Vagifem® 10 µg and 25 µg, respectively.

Table 18: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 19: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Corrected, N=27)

	E2			E1			E1S		
	AUC_{0-24}[b] (h.pg/ml)	$C_{ave(0-24)}$[c] (pg/ml)	%CV[a]	AUC_{0-24}[d] (h.pg/ml)	$C_{ave(0-24)}$[e] (pg/ml)	%CV[a]	AUC_{0-24}[f] (h.pg/ml)	$C_{ave(0-24)}$[g] (pg/ml)	%CV[a]
Day 1	146.66	6.11	50.65	66.99	2.79	124.94	1321.82	55.08	112.07
Day 14	81.06	3.38	98.56	77.91	3.25	129.20	2486.90	103.62	75.14
Day 83	36.61	1.53	209.81	-7.14	-0.30	-1232.56	-31.86	-1.33	-3536.09

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Baseline = 95.43, [c] Baseline = 3.98, [d] Baseline = 418.22, [e] Baseline = 17.43, [f] Baseline = 3836.51, [g] Baseline = 159.85

Table 20: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 21: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Corrected, N=27)

	E2			E1			E1S		
	AUC_{0-24}[b] (h.pg/ml)	$C_{ave(0-24)}$[c] (pg/ml)	%CV[a]	AUC_{0-24}[d] (h.pg/ml)	$C_{ave(0-24)}$[e] (pg/ml)	%CV[a]	AUC_{0-24}[f] (h.pg/ml)	$C_{ave(0-24)}$[g] (pg/ml)	%CV[a]
Day 1	393.72	16.41	32.13	116.16	4.84	60.27	2461.94	102.58	51.11
Day 14	365.78	15.24	42.18	208.40	8.68	46.23	4451.09	185.46	54.00
Day 83	177.42	7.39	93.26	45.52	1.90	270.00	836.03	34.86	157.37

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Baseline = 101.55, [c] Baseline = 4.23, [d] Baseline = 450.92, [e] Baseline = 18.79, [f] Baseline = 3276.38, [g] Baseline = 136.52

Table 22: Summary of E1 Baseline Derived for Vagifem® 10 µg

Variable	(b)(4)	N	Minimum	Median	Maximum	Mean	Std Dev	Coeff of Variation
AUCbase		29	37.89	394.40	903.95	418.22	181.42	43.38
CAVbase		29	1.58	16.43	37.66	17.43	7.56	43.38
AUC24		29	138.53	464.95	1309.60	485.21	217.67	44.86
AUC24_d		29	-51.15	72.75	405.65	66.99	83.70	124.94
CAVE		29	5.77	19.37	54.57	20.22	9.07	44.86
CAV_d		29	-2.13	3.03	16.90	2.79	3.49	124.94

Table 23: Summary of E1 Baseline Derived for Vagifem® (25 µg)

Variable	(b)(4)	N	Minimum	Median	Maximum	Mean	Std Dev	Coeff of Variation
AUCbase		28	168.59	460.35	814.90	450.92	158.64	35.18
CAVbase		28	7.02	19.18	33.95	18.79	6.61	35.18
AUC24		28	279.75	549.20	948.00	567.07	164.20	28.96
AUC24_d		28	-31.00	122.72	282.80	116.16	70.01	60.27
CAVE		28	11.66	22.88	39.50	23.63	6.84	28.96
CAV_d		28	-1.29	5.11	11.78	4.84	2.92	60.27

Estrone Sulfate (E1S)

Group AB (Vagifem 10 µg, Refer to Figure 5 and Table 24)

- Day -1: a pattern similar to E1 was observed for the evolution of mean plasma concentrations, with an initial slight decrease in mean plasma concentration until 15 hr then returning below T0 levels by 24 hr.
- Day 1: there was a rise in the mean plasma concentration of E1S with a mean C_{max} of 258.4 pg/ml at approximately 8 hr, as seen with E2 and then a decrease at 15 hr and a slight increase towards the end of the 24 hr period

- Day 14: the mean plasma concentration of E1S began decreased till 12 hr from where it slowly increased again for the remainder of the sampling period.
- Day 82: similar pattern to baseline with a slight increase in mean plasma concentrations.
- Day 83: mean plasma levels were observed to start rising from 12 hr.

Group CD (Vagifem 25 µg, Refer to Figure 6 and Table 24)

- Days -1, 82, and 83: followed similar pattern with an increase decrease in mean plasma concentration followed by an increase from 12 hr onwards
- Day 1: T_{max} at 10 hr is seen similar to that with the Vagifem® 10 µg treatment (at 8 hr)
- Day 14: mean plasma concentration decreases till 12 hr from where it slowly increases again for the remainder of the sampling period

Figure 5: Mean Concentration Profile of E1S in Plasma at All Days in Group AB (Vagifem® 10 µg)

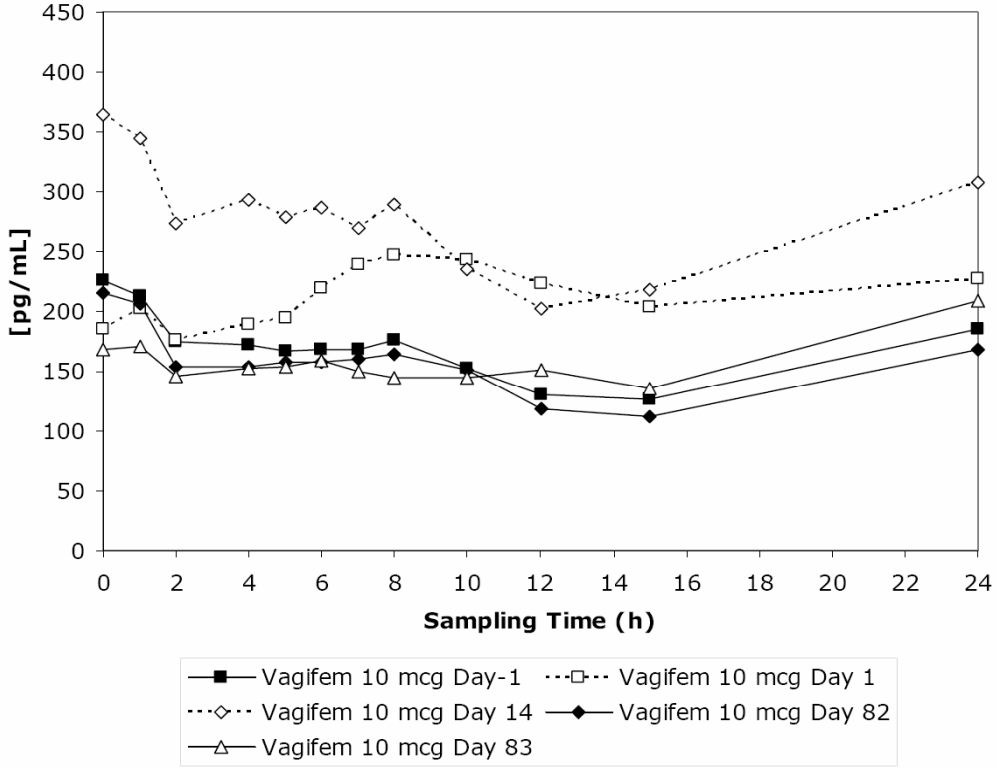


Figure 6: Mean Concentration Profile of E1S in Plasma at All Days in Group CD (Vagifem® 25 µg)

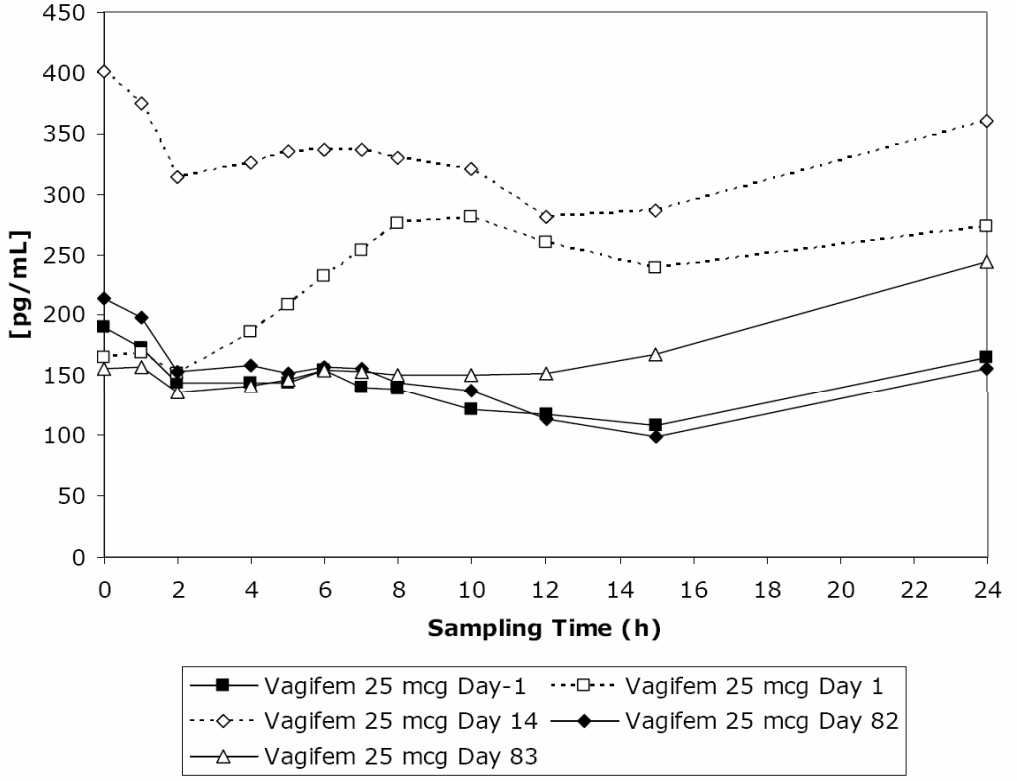


Table 24: Overall Geometric Mean (% CV) PK parameters from Plasma E1S Concentrations

Vagifem® 10 µg (Group AB), N=29					
	AUC_{0-24} (pg h/ml)	$C_{ave(0-24)}$ (pg/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	T_{max} (pg/ml)
Day -1	3345.3 (59.7)	139.4 (59.7)	226.7 (45.9)	113.3 (51.6)	0
Day 1	4482.3 (63.5)	186.8 (63.5)	258.4 (48.5)	140.2 (52.0)	8
Day 14	5599.6 (55.2)	233.3 (55.2)	356.5 (51.1)	167.4 (60.5)	1
Day 82	3030.1 (90.5)	126.3 (90.5)	223.1 (50.3)	116.0 (42.9)	1
Day 83	3371.5 (76.1)	140.5 (76.1)	215.8 (49.4)	120.3 (38.7)	12
Vagifem® (25 µg) (Group CD), N[a]=28 or 27					
	AUC_{0-24} (pg h/ml)	$C_{ave(0-24)}$ (pg/ml)	C_{max} (pg/ml)	C_{min} (pg/ml)	T_{max} (pg/ml)
Day -1	2842.9 (76.3)	118.5 (76.3)	193.0 (60.0)	112.7 (39.2)	0
Day 1	5022.1 (63.5)	209.3 (63.5)	334.8 (51.2)	130.9 (52.2)	12
Day 14	6794.3 (66.9)	283.1 (66.9)	415.2 (56.2)	220.3 (46.3)	5
Day 82	2923.9 (95.3)	121.8 (95.3)	214.4 (61.1)	108.4 (38.5)	1
Day 83	3597.8 (83.2)	149.9 (83.2)	241.8 (55.6)	114.8 (46.5)	24

[a] N=28 for treatments before Day 14 and N=27 for treatments from Day 14

Per the Division's request, the Sponsor has also submitted PK data for both uncorrected and corrected for baseline reported as arithmetic means. The baseline was derived by a full 24 hr PK profile performed at baseline on Day -1, (Day -1 baseline profile, starting 24 hr before first dosing at 0, 1, 2, 4,

5, 6, 7, 8, 10, 12, 15, and 24 hr). Tables 25-28 provide an overview of the data submitted. Tables 29 and 30 show how the baseline was derived for Vagifem® 10 µg and 25 µg, respectively.

Table 25: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 26: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 10 µg (Corrected, N=27)

	E2			E1			E1S		
	AUC_{0-24}[b] (h.pg/ml)	$C_{ave(0-24)}$[c] (pg/ml)	%CV[a]	AUC_{0-24}[d] (h.pg/ml)	$C_{ave(0-24)}$[e] (pg/ml)	%CV[a]	AUC_{0-24}[f] (h.pg/ml)	$C_{ave(0-24)}$[g] (pg/ml)	%CV[a]
Day 1	146.66	6.11	50.65	66.99	2.79	124.94	1321.82	55.08	112.07
Day 14	81.06	3.38	98.56	77.91	3.25	129.20	2486.90	103.62	75.14
Day 83	36.61	1.53	209.81	-7.14	-0.30	-1232.56	-31.86	-1.33	-3536.09

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Baseline = 95.43, [c] Baseline = 3.98, [d] Baseline = 418.22, [e] Baseline = 17.43, [f] Baseline = 3836.51, [g] Baseline = 159.85

Table 27: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Uncorrected, N=27)

	E2			E1			E1S		
	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]	AUC_{0-24} (h.pg/ml)	$C_{ave(0-24)}$ (pg/ml)	%CV[a]
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$

Table 28: Arithmetic Means of E2, E1, and E1S PK Parameters following Multiple Doses of Vagifem® 25 µg (Corrected, N=27)

	E2			E1			E1S		
	AUC_{0-24}[b] (h.pg/ml)	$C_{ave(0-24)}$[c] (pg/ml)	%CV[a]	AUC_{0-24}[d] (h.pg/ml)	$C_{ave(0-24)}$[e] (pg/ml)	%CV[a]	AUC_{0-24}[f] (h.pg/ml)	$C_{ave(0-24)}$[g] (pg/ml)	%CV[a]
Day 1	393.72	16.41	32.13	116.16	4.84	60.27	2461.94	102.58	51.11
Day 14	365.78	15.24	42.18	208.40	8.68	46.23	4451.09	185.46	54.00
Day 83	177.42	7.39	93.26	45.52	1.90	270.00	836.03	34.86	157.37

[a] CV: Coefficient of Variance for both AUC_{0-24} and $C_{ave(0-24)}$
[b] Baseline = 101.55, [c] Baseline = 4.23, [d] Baseline = 450.92, [e] Baseline = 18.79, [f] Baseline = 3276.38, [g] Baseline = 136.52

Table 29: Summary of E1S Baseline Derived for Vagifem® 10 µg

Variable (b)(4)	N	Minimum	Median	Maximum	Mean	Std Dev	Coeff of Variation
AUCbase	29	753.65	3549.90	10044.50	3836.51	2054.58	53.55
CAVbase	29	31.40	147.91	418.52	159.85	85.61	53.55
AUC24	29	607.20	4643.50	14723.00	5158.32	2763.43	53.57
AUC24_d	29	-753.95	1242.81	7680.00	1321.82	1481.38	112.07
CAV	29	25.30	193.48	613.46	214.93	115.14	53.57
CAV_d	29	-31.41	51.78	320.00	55.08	61.72	112.07

Table 30: Summary of E1S Baseline Derived for Vagifem® (25 µg)

Variable (b)(4)	N	Minimum	Median	Maximum	Mean	Std Dev	Coeff of Variation
AUCbase	28	0.00	3424.50	7191.00	3276.38	1866.25	56.96
CAVbase	28	0.00	142.69	299.63	136.52	77.76	56.96
AUC24	28	698.60	5379.75	12508.50	5738.32	2738.09	47.72
AUC24_d	28	698.60	2307.15	5317.50	2461.94	1258.18	51.11
CAV	28	29.11	224.16	521.19	239.10	114.09	47.72
CAV_d	28	29.11	96.13	221.56	102.58	52.42	51.11

Published literature estimates of the normal levels of postmenopausal endogenous E2 fall within the range of 5-25 pg/ml (DeCherney and Nathan, 2003). For the purposes of the Study VAG-1850, a plasma E2 concentration of 20 pg/ml was selected by the Sponsor as a threshold for systemic absorption of clinical interest. Selection of this threshold was based upon the Sponsor's belief that E2 levels below this value definitely fall within the normal range of postmenopausal plasma E2 concentrations, and would therefore not be expected to produce any clinically relevant systemic effects.

CONCLUSION

E2 administered into the vagina at repeated doses of 10 µg was found to display a PK profile that was globally similar in patterns to that following 25 µg administrations, while resulting in consistently lower mean plasma concentrations of E2, E1, and E1S. The mean E2 plasma concentration over 24 hr were always below 11 and 21 pg/ml for Vagifem® 10 and 25 µg, respectively, even after 14 days of daily administration. Although more than 50% of Vagifem® 25 µg subjects displayed average concentration above 20 pg/ml at Day 1, this decreased to 37% at Day 14 and to 15% after 10 weeks of maintenance. Overall, mean E2 concentration remained within the normal postmenopausal range also in the Vagifem® 25 µg group.

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A.2. Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	20-908	**Brand Name**	Vagifem
OCP Division	DCP3	**Generic Name**	Estradiol vaginal tablets
Medical Division	DRUP	**Drug Class**	Estrogen
OCP Reviewer	Chongwoo Yu, Ph.D	**Indication(s)**	(b)(4)
OCP Team Leader	Myong Jin Kim, Pharm. D.	**Dosage Form**	Tablet
		Dosing Regimen	10 µg of estradiol
Date of Submission	December 7, 2007	**Route of Administration**	Vaginal (local)
Estimated Due Date of OCP Review	August 7, 2008	**Sponsor**	Novo Nordisk Inc.
PDUFA Due Date	October 7, 2008	**Priority Classification**	Standard
Division Due Date	September 16, 2008		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		1		VAG-1850 (Systemic BA assessment): Vagifem 10 µg vs. 25 µg
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References		0		References are available upon request
Total Number of Studies		1		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	**No comments.**
Comments sent to firm?		
QBR questions (key issues to be considered)	1. Acceptability of the systemic BA study results of Vagifem 10 µg and 25 µg tablets. 2. Comparison of the Vagifem 25 µg estradiol PK profiles (current label vs. New proposed label) 3. Any formulation changes?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

* An Optional Intra-Division Clinical Pharmacology Briefing was held on Thursday, May 15, 2008. The attendees are as follows: HY Ahn, M-J Kim, S Apparaju, D Tran, L Lee, H Kim, J-I Lee, and T Van Der Vlugt.

Filing Memo

Clinical Pharmacology Review

NDA: 20-908
Compound: Vagifem (10 µg Estradiol)
Sponsor: Novo Nordisk Inc.

Date: 1/15/2008
Reviewer: Chongwoo Yu, Ph.D.

Introduction:

Vagifem 10 µg is a lower dose version of Vagifem (25 µg estradiol vaginal tablet). Initially, it was thought that a dose of 25 µg was necessary for the effective treatment of vaginal atrophy. However, the results from existing Vagifem clinical trials, in which a 10 µg estradiol vaginal tablet was included as comparator for Vagifem 25 µg, have suggested that the 10 µg estradiol tablet was also effective for the relief of the vaginal atrophy symptoms. Furthermore, the Sponsor believes that the long-term safety of the lower dose formulation would be at least comparable and perhaps improved compared to Vagifem 25 µg due to the lower estradiol systemic absorption.

Vagifem 10 µg tablets are intended for use in postmenopausal women with or without an intact uterus. The tablets are administered intravaginally using the applicator. The initial dose is one vaginal tablet daily for two weeks, and the maintenance dose is one vaginal tablet twice a week.

The Sponsor has submitted the results of a pivotal efficacy and safety clinical trial (VAG-2195) and a bioavailability (BA) clinical trial (VAG-1850). The estradiol drug substance and inactive excipients in Vagifem 10 µg are the same as those in Vagifem 25 µg.

Bioavailability:

The Sponsor has submitted the data from the BA clinical trial (VAG-1850) in which both Vagifem doses (10 and 25 µg) were used to compare the systemic absorption of estrogen. The Sponsor proposes to (b)(4) for both the 25 and 10 µg doses from the single bioavailability trial. Uncorrected baseline PK parameters were employed in the proposed label. The estradiol PK parameters for Vagifem 25 µg on the new proposed label based on results of Study VAG-1850 have lower values than those on the currently approved Vagifem (25 µg estradiol) label.

ADME (Absorption, Distribution, Metabolism, and Excretion):

New absorption data from the BA clinical trial (VAG-1850) in which both Vagifem doses (10 and 25 µg) were used to compare the systemic absorption of estrogen were submitted. The Sponsor relies exclusively on known distribution, metabolism, and excretion properties of Vagifem 25 µg.

Drug-drug interactions:

No new data is provided. No formal drug-drug interaction studies were conducted by the sponsor. *In vitro* and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital,

carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Special population:

No new data are provided. The sponsor did not conduct pharmacokinetic studies in any special population. However, the Sponsor states that Vagifem should not be used in women with known liver dysfunction or disease under the Contraindications section of the proposed label.

Clinical vs. to-be-marketed formulations:

According to the Sponsor, the estradiol drug substance and inactive excipients in Vagifem 10 µg are almost identical to those in Vagifem 25 µg except for the reduction of estradiol (b)(4) (b)(4). The batches used in clinical studies are produced in production size by the same formulation and with the same manufacturing equipment as intended for the market.

Method validation:

Study # VAG-1850 used a GC-MS assay to measure systemic estradiol levels and LC-MS/MS to measure estrone sulfate levels as necessary. This assay was validated and data are available for review.

Food Effect:

No new data is provided. The current label does not address food effect.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA (b)(4) is fileable.

Comments for sponsor:

- The absorption part of the Clinical Pharmacology section in the label including PK profiles and accumulation potential will be based on the relative BA study results.
- Please submit PK data of estradiol, estrone, and estrone sulfate for both corrected and uncorrected for the baselines including explanation of how the baseline corrected PK parameters were corrected.

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/s/

Chongwoo Yu
7/14/2008 09:14:20 AM
BIOPHARMACEUTICS

Myong-Jin Kim
7/17/2008 04:55:52 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020908Orig1s013

OTHER REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	September 26, 2008
To:	Scott Monroe, Director Division of Reproductive and Urologic Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Jinhee J. Lee, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Medication Error Labeling Review
Drug Name:	Vagifem (Estradiol Vaginal Tablets) 10 mcg
Application Type/Number:	NDA # 20-908/013
Applicant:	Novo Nordisk Inc.
OSE RCM #:	2008-164

Contents

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis (DMEPA) noted areas of vulnerability that could lead to medication errors with the container labels, carton and insert labeling of Vagifem. Improvements that could be made involve the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a January 17, 2008 request from the Division of Reproductive and Urologic Products, to review the applicant's container labels, carton and insert labeling. DMEPA reviewed the applicant's proposed container labels, carton and insert labeling submitted on December 7, 2007.

1.2 REGULATORY HISTORY

Vagifem is an extension of the Vagifem product line. Vagifem (NDA 20-908) was approved on March 26, 1999 for the treatment of atrophic vaginitis. This supplement provides for a lower strength (10 mcg) than is currently marketed (25 mcg) and for an expanded indication of use which includes the (b)(4)

1.3 PRODUCT INFORMATION

Vagifem (estradiol) is an estrogen indicated in the (b)(4) (b)(4) Vagifem should be administered vaginally. Vagifem will be available as 10 mcg in addition to the already existing 25 mcg vaginal tablets. Use of estrogen, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary. The recommended dose for the initial treatment is one tablet inserted vaginally once daily for two weeks. The maintenance dose is one tablet inserted vaginally twice weekly. Each Vagifem, 10 mcg and 25 mcg, will be contained in a disposable, single-use applicator, packaged in a blister pack. Cartons will contain 8 or 18 applicators with inset tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA conducting a label, labeling, and/or packaging risk assessment. The primary focus of the assessment is to identify and remedy potential sources of medication error prior to drug approval. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, dosage form, container quantity, expiration, and so on. The insert labeling is intended to communicate to

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the DMEPA staff analyzes reported misuse of drugs, the DMEPA staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. DMEPA uses Failure Modes and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

DMEPA reviewed the following labels and labeling submitted by the Applicant on December 7, 2007 and compared these to the 25 mcg labels and labeling available in the Annual Reported dated May 20, 2008. See Appendices A through D for pictures of the labels and labeling.

- Commercial Container Labels (10 mcg and 25 mcg - 18 and 8 tablet pack)
- Sample Container Labels (10 mcg and 25 mcg)
- Commercial Carton Labeling (10 mcg and 25 mcg - 18 and 8 tablet pack)
- Sample Carton Labeling (10 mcg and 25 mcg)
- Package Insert Labeling (no image)
- Patient Labeling (no image)

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Because Vagifem has been marketed since 1999, we conducted a search of the Adverse Event Reporting System (AERS) database to identify any medication errors associated with the use of Vagifem. The MedDRA Higher Level Terms (HLT) "Maladministration", "Medication Errors NEC", "Medication Errors Due to Accidental Exposures", "Medication Monitoring Errors", and the Preferred Terms (PT) "Overdose", "Accidental Overdose", "Multiple Drug Overdose", "Multiple Drug Overdose Accidental", "Pharmaceutical Product Complaint", and verbatim substance name "Vagife%" and tradename "Vagifem" were used as search criteria on July 22, 2008. Because the active ingredient, estradiol, is present in many other products, we limited our search parameters to include only those cases associated with the Vagifem product.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis as well as cases unrelated to the nomenclature and/or labeling of the product. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

3.1.1 General Comments

The container labels of the currently marketed 25 mcg and the proposed 10 mcg product look similar to each other.

The unit designation, microgram, is expressed using the micro symbol, µ.

3.1.2 Container Labels (Commercial and Sample)

See General Comments.

The strength and established name lack prominence.

3.1.3 Carton Labeling (Commercial and Sample)

See General Comments.

The strength is placed immediately after the proprietary name.

The dosage instructions present on the back display panel does not state the route of administration.

The inactive ingredients are not present on the labeling.

3.1.4 Package Insert Labeling

No comments.

3.1.5 Patient Labeling

The instruction steps and the figures utilize a number system to differentiate each step and figure.

Some of the figures are not located on the same page as the instruction.

3.2 ADVERSE EVENT REPORTING SYSTEM (AERS) SEARCH

Our AERS search retrieved three cases, two of which were related to either an adverse drug event or the quality of the drug product. In the remaining case, the reporter states that they may not have used the product correctly. No further details were provided about this case and this case appears to be an isolated event. It does not appear that the container labels, carton and insert labeling, nor the nomenclature contributed to any of the reported medication errors.

4 DISCUSSION

Our Risk Assessment noted areas that may be vulnerable to medication errors. Although we have not received reported errors to date citing these concerns, post-marketing experience with other products labeled similarly have resulted in actual errors. Additionally, because of underreporting of medication errors, we can not rule out the possibility that similar types of error may have occurred but were never reported.

DMEPA noted that the carton labeling for both strengths appear to be adequately differentiated. The proposed layout for the 10 mcg is in line with their new trade dress, however, we are concerned that if the 25 mcg labeling is changed in the near future to correspond with the 10 mcg trade dress, the carton labeling will no longer be adequately differentiated.

In contrast, the container labels look identical. The applicant uses a blue font color in the layout of both their 10 mcg and 25 mcg container labels, making it difficult to differentiate the two strengths from each other (see picture below). The contents of the Vagifem carton may potentially be separated from the packaging if only part of the carton is dispensed. This may be the case if a prescription is written for a quantity that does not adhere to how the drug product is marketed or if used in an inpatient facility. The vaginal tablets enclosed by this container label have the potential for confusion and selection error since the container labels closely resemble each other. Additionally, these two strengths are likely to be stored next to each other on the pharmacy shelf and we have concerns that confirmation bias may also contribute to the potential that the healthcare provider will select the wrong product strength. In order to decrease the potential for selection error, we suggest utilizing a different font color for one of the strengths, ensuring that the colors are distinct.

(b)(4)

The labels and labeling contain a dangerous unit designation (µg). The unit designation, microgram, is expressed using the micro symbol, µ, throughout the labels and labeling, which may be a source of confusion because it can be mistaken as "mg".[3] The microgram unit designation (µg) is being considered for addition to the JCAHO do-not-use list.[4]

Additionally, (b)(4) the carton labeling. This location is unconventional and inconsistent with how (b)(4) are typically presented. The standard way for this information to be presented is for (b)(4), (b)(4) item. We also note that the previously approved carton labeling displays (b)(4) (b)(4)" manner. Relocating this information may make it more difficult to locate and would be inconsistent from what consumers and healthcare practitioners are accustomed to.

Per 21 CFR 201.100 (b)(5), a qualitative listing of the inactive ingredients must be present on the carton labeling if the dosage route of administration is anything other than oral.

The instruction steps and figures presented in the patient labeling may be confusing because they utilize the same numbering system. It seems intuitive for the numbers to be coordinated with one another, however, they do not appear to match up. Additionally, the text oftentimes refers to figures that do not appear on the same page, further contributing to the confusing presentation. A clearer presentation might be for the figures to utilize letters of the alphabet while the instruction steps utilize numbers.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels, carton and insert labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEPA notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEPA believes the risks we

[3] Cohen, Michael (2007). *Medication Errors*. Second Edition. Washington DC: American Pharmacists Association. p153-171.

[4] http://www.jointcommission.org/patientsafety/donotuselist/

have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.1 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, OSE project manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

Based upon our assessment of the labels and labeling, DMEPA identified the following areas of needed improvement.

1. Replace all unit designations expressed as "µg" with "mcg" when expressed with a strength to be consistent with FDA's policy on excluding dangerous abbreviations and symbols from approved labels and labeling. FDA launched a campaign on June 14, 2006 warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols (e.g. trailing zeros).
2. Consider revising the carton labeling so that the (b)(4) (b)(4) In its current location, it may be more difficult to locate the (b)(4) because it is inconsistent from what consumers and healthcare practitioners are used to.
3. List the inactive ingredients on the carton labeling per 21 CFR 201.100 (b)(5).
4. The numbering in the patient labeling for the instructions is confusing in presentation and the figures are not coordinated with the text. Consider labeling figures alphabetically and reserve the numbers for the instruction steps.

Eight pages have been redacted as (b)(4), draft labeling, immediately following this page.

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/s/

Jinhee Jahng
9/26/2008 11:12:54 AM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
9/26/2008 01:46:10 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/26/2008 02:30:16 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 3, 2008

TO: George Lyght, Regulatory Project Manager
Theresa Van Der Vlugt, M.D., Medical Officer
Division of Reproductive and Urologic Products (DRUP)

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-908/013

APPLICANT: Novo Nordisk, Inc.

DRUG: Vagifem® (estradiol vaginal tablet)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of postmenopausal atrophic vaginitis

CONSULTATION REQUEST DATE: February 13, 2008

DIVISION ACTION GOAL DATE: October 7, 2008

PDUFA DATE: October 7, 2008

I. BACKGROUND

Clinical investigator inspections were requested at two clinical sites that performed studies for which the sponsor submitted data in NDA 20-908/013. The clinical investigator inspections were conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocol VAG-2195 entitled "A 12 month double-blind, randomized, parallel-group, placebo-controlled, multi-center trial to investigate the efficacy and safety of Vagifem Low Dose (10 µg 17 β-estradiol vaginal tablet) for the treatment of postmenopausal atrophic vaginitis symptoms."

The efficacy of Vagifem 10 µg in the (b)(4) (b)(4) was established in a pivotal trial, VAG-2195, which was provided in this submission. This pivotal study was selected for inspection. VAG-2195 was a double-blind, randomized, multi-center, placebo-controlled, parallel group trial conducted to evaluate the safety and efficacy of Vagifem 10 µg compared to placebo during a 52-week study period. VAG-2195 was a prospective study conducted at 51 U.S. sites and 5 Canadian sites.

Basis for Site Selection: Two clinical sites (Drs. Harrell and Koltun) were inspected. Based on the number of subjects randomized and treated, the number of discontinuations during the double-blind portion of Study VAG-2195 (the primary period for safety and efficacy) and the number of discontinuations during the open-label portion (observed for safety), and the number of protocol violations, these two clinical sites were recommended for inspection. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)/# of subjects	Inspection Date	Final Classification
Dr. Lonnie Clayton Harrell Metrolina Medical Research 1700 Abbey Place Suite 209 Charlotte, NC 28209	VAG-2195 13 subjects	3/24-25/2008	NAI
Dr. William Koltun Medical Center for Clinical Research 9040 Friars Road San Diego, CA 92108	VAG-2195 19 subjects	3/19 - 4/1/2008	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Dr. Lonnie Clayton Harrell
Charlotte, NC

a. What was inspected?

A total of 13 were randomized into the study. The FDA investigator performed a complete review of all 13 subjects' files. The inspection was conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The goals of inspection included validation of submitted data and compliance of study activities with federal regulations. Complete files were reviewed for all subjects including study regulatory records, case report forms (CRFs), and other study-specific source documents filed with the CRFs. Records were reviewed for informed consent, IRB approval, drug accountability, diagnosis, and entry criteria. Source documents were compared with data listings provided in the NDA for verification of safety and efficacy endpoints. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

In general, Dr. Harrell complied with protocol specified requirements. There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

Data generated for protocol VAG-2195 at this clinical site appear acceptable for use in support of NDA 20-908/013.

2. Dr. William Koltun
San Diego, CA

a. What was inspected?

A total of 21 subjects were screened, 19 were randomized into the study and 12 completed the study. The FDA investigator performed a complete review of 12 subjects'

records. The FDA investigator reviewed the source documents and case report forms (CRFs), and compared these with data listings provided by the sponsor as part of the NDA submission. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events. The inspection encompassed an audit of all subjects' consent forms.

b. General observations/commentary:

There were no significant inspectional findings that would adversely impact data acceptability. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. No underreporting of adverse events was noted. Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms.

In general, Dr. Koltun complied with protocol specified requirements. However, there were several instances where the inspection documented that Dr. Koltun was in noncompliance with regulations pertaining to protocol compliance, informed consent, and drug accountability records, specifically:

1. Dr. Koltun did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

   The protocol required eligible subjects to have at least three urogenital symptoms and at least one of them has to be a moderate to severe symptom as identified by the subject during the last week of the screening period. The Urogenital Symptom Questionnaire for subject # (b)(6) at baseline visit documented either "mild" or "none" for each of the subject's urogenital symptoms. However, the subject was enrolled in the study in violation of the protocol.

2. Dr. Koltun did not obtain informed consent from subjects in accordance with the provisions of 21 CFR Part 50 [21 CFR 312.60].

   The IRB approved an amended informed consent form (version 5.0) on 3/2/06. However, this amended informed consent was not signed and dated by subject # (b)(6) who was randomized in the study on 5/15/06.

3. Dr. Koltun did not maintain adequate records for disposition of the investigational drug [21 CFR 312.62(a)].

   i. Drug accountability records for subject # (b)(6) document that 165 tablets were dispensed to the subject; however, the returned drug log documents a total of

150 tablets.

ii. Drug accountability records for subject # (b)(6) documents that 135 tablets were dispensed to the subject; however, the returned drug log shows a total of 150 tablets.

There were no significant inspectional findings that would adversely impact data acceptability. No underreporting of adverse events was noted. Data in sponsor-provided data listings were supported by data in source documents and case report forms.

c. Assessment of data integrity:

The review division may wish to exclude from efficacy analyses the subject who failed the study eligibility criterion as stated above. Overall, data generated for protocol VAG-2195 at this clinical site appear acceptable for use in support of NDA 20-908/013.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there were several instances where the inspection documented that Dr. Koltun was in noncompliance with regulations pertaining to protocol compliance, informed consent, and drug accountability records. In general, for the two clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol.

No underreporting of adverse events was noted. Overall, data generated for protocol VAG-2195 at these clinical sites appear acceptable for use in support of NDA 20-908/013.

{See appended electronic signature page}

Jose Javier Tavarez, M.S.
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Constance Lewin
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MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 21, 2008
To:	Scott Monroe, M.D., Director Division of Reproductive & Urologic Products (DRUP)
Through:	Jodi Duckhorn, M.A. Team Leader Patient Labeling and Education Team Division of Risk Management (DRISK)
From:	Nancy Carothers Patient Product Information Specialist Patient Labeling and Education Team Division of Risk Management (DRISK)
Subject:	Review of Patient Labeling for a low dose product
Drug Name(s):	Vagifem (estradiol vaginal tablets)
Application Type/Number:	NDA 20-908/013
Submission Number:	#SE2013
Applicant/sponsor:	Novo Nordisk Inc.
OSE RCM #:	2008-149

1 INTRODUCTION

Vagifem® is an estrogen product indicated for [redacted]. It is indicated to [redacted], and is supplied as a tablet with applicator for local vaginal treatment. Vagifem was first approved at the 25 mcg dose on March 26, 1999.

The FDA encouraged the development of the lowest doses and exposures for estrogens and progestins, and the sponsor has developed a 10 mcg. dose of Vagifem®. On December 7, 2007, the sponsor submitted a supplement (#SE2013) for the lower tablet strength of 10 mcg.

The Division of Reproductive and Urologic Products requested that the Patient Labeling and Education Team use the Professional Information (PI) and Patient Package Insert (PPI) for the original 25 mcg. dose to review the 10 mcg. dose. This product has not been previously reviewed by the Office of Surveillance and Epidemiology.

2 MATERIAL REVIEWED

The Vagifem® PI/PPI for the 25 mcg. Dose, revised October 2007 (version 4.4).

3 DISCUSSION

A PPI is required for this product. The purpose of the PPI is to enhance appropriate use of and to provide important risk information about medicines. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review we have:

- simplified the wording where possible,
- made the information in the PPI consistent with the PI,
- removed unnecessary and redundant information in the PPI,
- assessed the Patient Instructions for Use,
- ensured that the PPI is consistent with the November 2005 (Revision 4) *Draft Guidance for Industry: Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for health Care Providers and Patient Labeling*, based on the WHI study.

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the review division are ***bolded, underlined, and italicized***.

We are providing to the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI.

4 CONCLUSIONS AND RECOMMENDATION

- For consistency, we suggest adding the Patient Instructions for Use that appear in the original PPI to the PI. The PPI and PI should have consistent information.
- We suggest moving the instructions to the end of the PPI to be consistent with other patient labeling materials.
- We recommend including information on 10 mcg. dosing and scheduling and on the number of doses in each carton, if this is different from the information provided for the 25 mcg. dose.
- We added the following statement to the end of the section, "General information about the safe and effective use of Vagifem."

  "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

  This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse events on Labeling for Human Drug Products in Federal Register Vol. 73, No.2, p.402-404, 1/3/2008).

Please let us know if you have any questions

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/s/

Nancy B Carothers
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DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/21/2008 04:58:13 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	03/06/2008
To:	Scott Monroe, M.D., Director Division of Reproductive and Urologic Products
From:	Adrienne M. Rothstein, Pharm.D., Safety Evaluator Division of Adverse Event Analysis
Through	Melissa M. Truffa, R.Ph., Safety Evaluator Team Leader Division of Adverse Event Analysis
Subject:	Post-marketing Safety Review of Vagifem
Drug Name(s):	Vagifem® (estradiol vaginal tablets)
Submission Number:	#SE2013 - Supplement for a lower dose product
Application Type/Number:	20-908
OSE RCM #:	2008-149

CONTENTS

EXECUTIVE SUMMARY

The Division of Adverse Event Analysis (DAEA) was consulted for a safety review of Vagifem® (estradiol vaginal tablets) related to a supplement for a lower tablet strength (10 mcg) than the currently approved tablet strength (25 mcg). A recent draft guidance from the FDA encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known.

For this summary, data mining scores and AERS reports for Vagifem (trade name) were reviewed. The preferred terms with the highest data mining scores and the most commonly reported preferred terms in the AERS database were reviewed and compared against the current labeling for Vagifem. This review did not identify any new or unexpected adverse event terms for consideration as additions to the current labeling.

1 BACKGROUND

1.1 INTRODUCTION

DAEA was consulted for a post-marketing safety review for Vagifem® (estradiol vaginal tablets) related to a December 7, 2007 supplement for a lower dose of 10 mcg. The approved dosage regimen for Vagifem is 25 mcg initiated as one tablet inserted vaginally once daily for two weeks. The maintenance dose is one tablet inserted vaginally twice weekly.

The indication for use for this product is (b)(4) (b)(4).

This Vagifem safety review will examine potentially significant data mining scores and the most commonly reported adverse event terms in the AERS database. This product has not been previously reviewed by the Office of Surveillance and Epidemiology.

1.2 REGULATORY HISTORY

Vagifem was approved on March 26, 1999 at a dose of 25 mcg. On December 7, 2007, the sponsor submitted a supplement (SE2-013) for a lower tablet strength of 10 mcg.

2 METHODS AND MATERIALS

2.1 DATA MINING

The term 'data mining' refers to the use of computerized algorithms to discover hidden patterns of associations or unexpected occurrences (i.e. 'signals') in large databases. These signals can then be evaluated for intervention as appropriate.

The Bayesian algorithm used for the data mining analysis was the Multi-Item Gamma Poisson Shrinker (MGPS).[1, 2] This algorithm analyzes the records contained in large post-marketing drug

[1] DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

[2] Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

safety databases and then quantifies potential drug-event associations by producing a ranked set of values or scores which indicate varying strengths of reporting relationships between drugs and events. The EB05 is an estimated lower 95% "confidence limit" for the adjusted observed-to-expected (N/E) ratio calculated by the data mining algorithm. EB05 is useful for ensuring with high probability that the observed-to-expected ratio for a particular item set (e.g., drug-event combination) *exceeds* a certain value. Thus, using an EB05 ≥ 2 as a signal definition indicates 95% confidence that a drug-event combination in question occurs at least at twice the expected rate when considering all other drugs and events in the database.

Search Strategy:

The WebVDME 6.0 data mining application from Lincoln Technologies was searched on February 14, 2008 using the trade name "Vagifem." All preferred terms (PTs) with an EB05 ≥ 2.0 were retrieved (these reports were not reviewed individually).

2.2 AERS SELECTION OF CASES

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. FDA receives adverse drug reaction reports from manufacturers as required by regulation, including both foreign and domestic reports. Health care professionals and consumers send reports voluntarily through the MedWatch program. Based on data entry rules, the adverse event reports are entered into the AERS database. All reported adverse event terms are coded using a standardized international terminology, MedDRA (Medical Dictionary for Regulatory Activities).

Search Strategy:

The AERS database was searched as follows:

- Any report with the suspect drug Vagifem listed as the Trade Name (search date 2/13/08)

No attempt was made to eliminate duplicates or reports retrieved inadvertently.

3 RESULTS

3.1 DATA MINING

All preferred terms (N = 3) with an EB05 score ≥ 2.0 are presented in **Table 1**. These preferred terms were all related to breast cancer.

Table 1. Data Mining Scores with EBO5 Score ≥ 2.0 for Vagifem as Trade Name

Preferred Term (PT)	High Level Term (HLT)	N	EB05
Breast cancer female	Breast and nipple neoplasms malignant	83	23.7
Marital problem ("loss of consortium")	Family and partner issues	4	6.7
Breast cancer	Breast and nipple neoplasms malignant	19	3.3

3.2 ADVERSE EVENT CASES

A search of the AERS database for any report with the suspect drug Vagifem listed as the Trade Name retrieved 188 reports. The most commonly reported PTs are listed in **Table 2** below. These events were compared against the current labeling; the only unlabeled events are anxiety and psychiatric symptom.

Table 2. Most Commonly Reported PTs for Vagifem (Trade Name)
(N = 188 reports in AERS)

Preferred Term (PT)	Count of PTs	% of Total
Breast Cancer Female	85	45.21
Breast Cancer	19	10.11
Pain	14	7.45
Anxiety	11	5.85
Oestrogen Receptor Assay Positive	6	3.19
Progesterone Receptor Assay Positive	6	3.19
Urticaria	6	3.19
Psychiatric Symptom	5	2.66
Vaginal Haemorrhage	5	2.66

4 DISCUSSION

4.1 DATA MINING

For the Data Mining analysis, MedDRA preferred terms with an EB05 score ≥ 2.0 for the tradename Vagifem were retrieved (see **Table 1)**. These preferred terms were then compared against the adverse event terms listed in the current prescribing information. All the preferred terms with the highest data mining scores presented in **Table 1** relate to breast cancer.

The current labeling for Vagifem contains a **BOXED WARNING** that estrogen-plus-progestin increase the risk of invasive breast cancer in post-menopausal women receiving *oral* conjugated estrogens with medroxyprogesterone acetate, among other events. The **BOXED WARNING** follows the recommendations in the draft guidance for industry "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommended Prescribing Information for Health Care Providers and Patient Labeling" (dated November 2005).

Thus, data mining did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling.

4.2 ADVERSE EVENT CASES

The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Hence, when considering counts of cases generated from AERS, it should be realized that case reports cannot be used to calculate incidence or estimates of drug risk for a particular product, as reporting of adverse events is a voluntary process, and underreporting exists. Further, because of the multiple factors, which influence reporting, comparisons of drug safety cannot be made from these data. Some of these factors include the length of time a drug is marketed, the market share, size and sophistication of the sales force, publicity about an adverse reaction and regulatory actions (e.g. Women's Health Initiative study results).

It should also be noted that in some reported cases, the clinical data are incomplete, and there is no certainty that these drugs caused the reported reactions. A given reaction may actually have been due to an underlying disease process or to another coincidental factor. Further, these data often contain duplicates and manual review is required to distinguish unique patients.

A search of the AERS database for any report with the suspect drug Vagifem listed as the Trade Name retrieved 188 reports in AERS. The most commonly reported PTs in this review were

breast cancer female, breast cancer, pain, anxiety, estrogen receptor assay positive, progesterone receptor assay positive, urticaria, psychiatric symptom and vaginal hemorrhage. These events were compared against the current labeling. Only the events of anxiety and psychiatric symptom were unlabeled and were evaluated further.

The term psychiatric symptom is too non-specific to be meaningful. Eleven reports of anxiety were retrieved, which is not particularly noteworthy because anxiety disorders are the most common class of psychiatric disorders.[3] Thus, the searches of the AERS database did not identify any new or unexpected adverse event terms for consideration as additions to the proposed labeling.

5 CONCLUSION

The review of data mining scores and the search of the AERS database for Vagifem did not identify any unlabeled adverse event terms for consideration as additions to the proposed labeling.

6 RECOMMENDATIONS

DAEA has no labeling recommendations based on this postmarketing safety review.

[3] Chapter 196. Anxiety Disorders. In: Merck Manual of Diagnosis and Therapy, 18th edition (2006).

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/s/

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