CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20908

MEDICAL REVIEW(S)

Medical Officer's NDA Review

NDA Number: 20-908

Applicant: Novo Nordisk Pharmaceuticals, Inc.
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MAR 25 1999

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Date Review Completed: February 26, 1999

Date Review Revised: March 16, 1999

Date Review Finalized: March 25, 1999

I. General Information:

A. Name of Drug:

1. Established Name: 17-β estradiol
2. Proprietary Name: Vagifem
3. Chemical Name: estra-1,3,5(20)-triene-3, 17β-diol hemihydrate

B. Pharmacologic Category: Estrogen

C. Proposed Indication: Treatment of atrophic vaginitis, a component of urogenital syndrome associated with the estrogen deficiency of menopause.

D. Dosage Form and Route of Administration: Tablets for intravaginal administration using a supplied applicator.

E. Strength of Tablet: 25 micrograms

F. Dosage: The initial dose is one tablet once daily for two weeks. The maintenance dose is one tablet twice weekly.

G. Related Drugs: Premarin Vaginal Cream and Ortho Dienestrol Cream.

II. Manufacturing Controls: Please refer to chemist's review.

III. Pharmacology: Please refer to pharmacologist's review dated October 21, 1998.

IV. Clinical Background: Vagifem is a low-dose estrogen-containing vaginal tablet containing 25 micrograms of 17β-estradiol for the treatment of atrophic vaginitis associated with estrogen deficiency of menopause. Symptoms are primarily irritative and are often accompanied by vaginal dryness and dyspareunia. The vaginal epithelium appears thin. The pH exceeds 6 (as it does in all estrogen - deficient women whether or not they have symptoms). The most effective treatment is either topical or oral estrogen. Topical treatment is suitable for postmenopausal women who are not experiencing hot flashes or profuse sweating.

V. Regulatory Background:

A. IND

B. The applicant was informed by letter February 13, 1995 that their proposal of one large U.S. placebo-controlled study was acceptable with the Canadian study serving as the second pivotal study.

C. A pre-NDA meeting with the applicant occurred April 29, 1997 and the applicant agreed to incorporate recommendations from the meeting into the NDA submission.

VI. Foreign Marketing History: Vagifem was first approved in Denmark in March, 1990. Since that date through March 31, 1998, boxes of Vagifem tablets (15 tablets per box) have been sold. The applicant has received complaints of six adverse events through their post marketing reporting system. Two of the six events were injuries related to the applicator (ruptured vaginal fornix in Finland and ruptured suture in the anterior vaginal wall 6 weeks following a vaginal hysterectomy in Australia). The other four events were endometrial hyperplasia, malignant endometrial neoplasm, malignant breast neoplasm, and leg thrombosis. There were an additional 14 adverse events reported from other foreign clinical trials, none of which were attributed to Vagifem. The drug is now marketed in 53 countries. Over million doses have been sold. Two countries have refused to approve Vagifem for marketing. The Canadian Therapeutics Products Directorate deemed the absorption data in the application as insufficient in March, 1994. A study has been completed and the final report was filed to the Canadian authorities in March, 1998. The application is currently under review. The French health authorities refused approval of Vagifem on March 14, 1995. They felt that the administration schema was not justified, the maximum safe dose was not

determined, and the risk of endometrial hyperplasia could not be eliminated without associated progestogen treatment.

VII. Consultations: Please refer to Statistician's Review

VIII. Clinical Studies: Nineteen clinical trials were conducted with Vagifem in the United States, Canada, Europe and Australia. Eight of these trials were adequate and well controlled and considered as primary source data. Of these eight trials, two were pharmacokinetic trials and six were efficacy and safety trials. The other eleven trials are considered as secondary source data. Information is limited or incomplete for these trials. Case report forms and full study reports for these 11 trials are not available and, therefore, cannot be analyzed.

The six efficacy and safety trials are divided into four groups and include a total of 604 women, 386 of whom were treated with Vagifem.

— 9/USA and 5/CAN are the pivotal adequate and well controlled trials designed to assess the efficacy and safety of Vagifem. Study 9/USA was conducted under IND

— 33/ATR is a supportive trial designed to assess the efficacy and safety of Vagifem as compared to placebo.

— 12/USA, 6 CAN, and 7/END are trials designed to assess long-term maintenance response and safety of Vagifem. Study 12/USA was conducted under IND

— 7/END is a trial designed to compare two dosage regimens of Vagifem.

A. Study 9/USA. A Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Multicenter Study Comparing the Efficacy and Safety of 17-β Estradiol 10 micrograms and 25 micrograms (Vagifem) Doses in Treatment of Estrogen Deficiency - Derived Atrophic Vaginitis

1. Investigators and Sites:

Gloria Bachmann,	New Brunswick, New Jersey
Guillermo Davila,	Denver, Colorado
M. Wayne Heine,	Tucson, Arizona
Rogerio Lobo,	Los Angeles, California
Lila Nachtigall,	New York, New York

Morris Notelovitz,	Gainesville, Florida
Stephen Gordon,	Atlanta, Georgia
Mildred Farmer,	St. Petersburg, Florida
Stephen Stewart,	Olympia, Washington

2. Objective of the Study:
To evaluate the efficacy and safety of 17-β estradiol, 10 micrograms and Vagifem (17-β estradiol, 25 micrograms) with placebo during three months of treatment of estrogen deficiency-derived atrophic vaginitis.

3. Rationale for the Study:
With the decline in endogenous estrogen production during the menopause, the vagina (and other estrogen-dependent tissues) gradually undergo atrophic changes. The vaginal epithelium becomes thin and pale. The most effective treatment is either topical or systemic estrogen.

4. Method of assignment to Treatment:
Subject who fulfilled inclusion criteria after a maximum 4-week screening period were randomized to receive either Vagifem, a 10 microgram estradiol vaginal tablet, or placebo, according to a 2:2:1 randomization scheme.

5. Number of Subjects:
Two hundred thirty subjects were randomized; 91 to Vagifem, 92 to estradiol 10 micrograms, and 47 to placebo.

6. Duration of Clinical Trial:
After a 4-week screening period, subjects entered a 12 week period of treatment with either active drug or placebo.

7. Inclusion Criteria:

— Postmenopausal women 45 years of age or older

— Presence of moderate or severe vaginal dryness and soreness

— At least 12 months past natural menopause in nonhysterectomized subjects

- Serum estradiol ≤ 20 pg/ml (changed from ≤ 25 pg/ml)
- Subjects with intact uteri must have endometrial thickness of ≤ 5mm by pelvic ultrasound
- No more than 5% superficial cells by vaginal cytology evaluation (lateral vaginal wall smear)
- Serum FSH ≥ 40 mIU/mL (deleted December 1, 1994)
- Willing to give written informed consent to participate in the study

8. Exclusion Criteria:

- Known, suspected, or past history of carcinoma of the breast
- Known, suspected, or past history of hormone-dependent tumor
- Genital bleeding of unknown etiology
- Acute thrombophlebitis or thrombroembolic disorders or a past history of these conditions, associated with previous estrogen use
- History of treatment with DES (diethylstilbestrol)
- Use of any type of vaginal, vulvar, or oral homeopathic preparation seven days prior to visit 2
- Corticosteroid or sex hormones within 8 weeks of visit 2
- Known or suspected vaginal infection requiring further treatment
- Any serious disease or chronic condition that might interfere with study compliance
- Subjects who are unwilling to agree to the provisions of the protocol

- Known or suspected allergy to the test drug or the vaginal tablet constituents
- Exposure to any investigational drug within the past 30 days
- Creatinine ≥ 1.4 mg/dL
- Bilirubin ≥ 1.2 mg/dL
- SGOT ≥ 50 u/L
- Hemoglobin < 11.5 g/dL

9. Trial Period:
August 12, 1994 through July 14, 1995

10. Dose and Mode of Administration:
The test products were two doses of 17-Bestradiol, one 10 micrograms and the other 25 micrograms (Vagifem). The tablets were inserted intravaginally with a supplied applicator once daily for the first two weeks, then twice weekly (Sunday and Thursday) for 10 weeks. The placebo tablet was identical in appearance to the active tablets and was administered in the same manner as the active tablets.

11. Efficacy Assessments:
The primary efficacy variable was relief of vaginal symptoms based on the change in the composite score at week 7, last observation carried forward. The composite score was calculated as the average of the scores of three symptoms (vaginal dryness, soreness, and irritation). Symptoms recorded at baseline and at subsequent visits were graded on a four-point scale as none, mild, moderate, or severe. Scores were assigned to each grade as 0,1,2, and 3 respectively. Vaginal health, vaginal cytology, and urethral cytology were secondary efficacy endpoints. Improvement in vaginal health as assessed by the investigators included assessments of secretions, epithelial integrity, surface thickness, color, and pH at baseline and at each intreatment visit. Maturation of vaginal and urethral mucosa cells was evaluated based on the percentage of

superficial, intermediate, and parabasal cells seen at baseline compared with each intreatment visit.

12. Safety Assessments:
Adverse events observed by the investigator or reported by the subjects were recorded and evaluated. C.B.C.s, blood chemistries, urinalyses, and serum hormone levels were recorded and evaluated. Endometrial biopsies were collected from nonhysterectomized subjects with the Milex or Wallach Endocell samplers at the end of the study and evaluated by two independent pathologists, blinded to treatment group and each other's interpretation.

13. Disposition of Subjects:
Four hundred thirty-three subjects were screened. Two hundred thirty subjects were randomized and received treatment. The number of subjects at each investigational site is shown in Table 1.

Table I
(Sponsor's Table 6.1a)
Number of Treated Subjects by Investigator

Investigator	Placebo	E2 10 micrograms	Vagifem	Total
Bachman	7	14	12	38
Davilla	5	10	10	25
Heine	9	18	19	46
Lobo	0	0	1	1
Nachtigal	4	8	7	19
Notelovitz	10	18	19	47
Funk	3	6	5	14
Farmer	9	17	17	43
Stewart	0	1	1	2
Total No. of Pts.	47	92	91	230

Of the 230 subjects treated, 195 completed the study, 39 (83%) in the placebo group, 74 (80%) in the estradiol 10 micrograms group, and 82 (90%) in the Vagifem group. The study completion status and percentages of subjects who withdrew from the study are shown in table 2.

Table 2
Sponsor's Table 6.1b
Study Completion Status

	Placebo	Estradiol 10μ	Vagifem
Total Randomized	47	92	91
Total Completed	39 (83.0%)	74 (80.4%)	82 (90.1%)
Reason for not Completing			
Adverse Event	1 (2.1%)	6 (6.5%)	4 (4.4%)
Medical Problems	0 (0.0%)	1 (1.1%)	0 (0.0%)
Noncompliance	3 (6.4%)	10 (10.9%)	4 (4.4%)
Ineffective Therapy	2 (4.3%)	0 (0.0%)	0 (0.0%)
Other	2 (4.3%)	1 (1.1%)	1 (1.1%)
Total Noncompletions	8 (17.0%)	18 (19.6%)	9 (9.9%)

14. Protocol Deviations:
The majority of screening violations were superficial cells exceeding the 5% limit. The variability in % cytology categories at screening, at baseline, and during placebo treatment discourages stringent use of this entry criterion.

15. Demographic and Background Features:
Vaginal symptoms at baseline were similar in both the Vagifem and placebo treatment arms.

Table 3 summarizes subject demographic and background information. All subjects were 46 years of age and older (mean age approximately 58 years) and almost equally distributed between those with uterus intact versus post hysterectomy. Most of the subjects were white. The mean time since last menses was approximately 14 years for all three groups. There were no differences between the Vagifem group and the placebo group for any demographic or baseline variables.

Table 3
Sponsor's Table 6.3
Demography and Background Features (All Subjects)

	Placebo	Estradiol 10μ	Vagifem
Total Subjects Randomized	47	92	91
Age (years)			
N	47	92	91
Mean (SD)	57.6 (4.8)	57.7 (6.5)	58.3 (7.4)
Min-Max	50-70	46-79	46-78
Race			
White, N (%)	41 (87.2)	83 (90.2)	88 (96.7)
Non-White, N (%)	6 (12.8)	9 (9.8)	3 (3.3)
Asian	2	0	0
Black	1	6	1
Hispanic	2	2	2
Mexican	1	0	0
Native	0	1	0
Time Since last menses (years)			
N	47	92	91
Mean (SD)	13.6 (8.1)	13.5 (7.8)	14.8 (9.6)
Min-Max	1-33	1-34	1-40
Hysterectomy			
Yes, N (%)	23 (48.9)	44 (47.8)	42 (46.2)
No, N (%)	24 (51.1)	48 (52.2)	49 (53.8)

16. Extent of Exposure:
Ninety two subjects were treated with estradiol, 10 micrograms, (Patient 255 did not have a drug accountability record and is not listed in Table 4), 91 subjects with Vagifem, and 47 subjects with placebo. The cumulative number and percentage of subjects completing specified time periods is shown in Table 4.

Table 4
(Sponsor's Table 7)
Cumulative Duration of Treatment (Weeks)

	Placebo		E_2 10μ		Vagifem	
Weeks of Treatment	N	%	N	%	N	%
< 2	0	0.0	5	5.5	3	3.3
3-4	1	2.1	9	9.9	6	6.6
5-6	2	4.2	10	11.0	7	7.7
7-8	5	10.6	16	17.6	10	11.0
9-10	8	17.0	18	19.8	11	12.1
11-12	37	78.7	67	73.6	62	68.1
13-14	46	97.1	90	98.9	90	98.9
15-16	47	99.2	91	100.0	91	100.0

17. Results:

a. Efficacy:
The average scores of three symptoms (vaginal dryness, soreness and irritation) was prespecified as a composite score.

Vagifem was superior to placebo in the relief of symptoms of the dryness, soreness, and irritation associated with atrophic vaginitis. Mean change in composite score of vaginal symptoms from baseline was greater for the Vagifem-treated group (-1.22) compared with placebo (-0.85), p=.016. This change of symptoms seen at week 7 is shown in Table 5.

Table 5
(Sponsor's Table 8.2.1a)
Relief of Symptoms - Mean Change in Composite Score of Three Symptoms at Week 7 (LOCF)

Treatment	N	Base	Wk 7	Mean Change from Baseline (SE)	Difference	p-value
Placebo	47	1.93	1.08	-0.85 (0.15)	-0.37	0.016
Vagifem	91	1.85	0.63	-1.22 (0.09)		

The difference in mean change for the composite symptom score from baseline between placebo and Vagifem was only 0.37. A difference continued to

the end of the study. At week 12, the mean scores were 1.06 and 0.46 for the placebo and Vagifem groups, respectively, a change from baseline of -0.86 for placebo and -1.41 for Vagifem, a difference of -0.55 (p-value=0.011).

Descriptive statistics showing the mean change from baseline in individual vaginal symptoms scores over time are shown in Table 6. The changes from baseline to week 12 were consistently greater in the Vagifem group than in the placebo group for the individual symptoms of dryness, dyspareunia, irritation, and soreness. Changes were comparable for vaginal discharge since most of the subjects did not have this symptom when they were randomized. Treatment-by-center interactions were noted. Center number 2 was the only center where placebo was superior to Vagifem. Center number 8 was the only center where placebo yielded a very poor response. This resulted in a large treatment difference (1.22) at center 8 in favor of Vagifem.

Table 6
(Sponsor's Table 10)
Vaginal Symptoms - Mean Changes Over Time From Baseline

		Placebo		Vagifem 25	
Symptom	Visit	N	CHG (SD)	N	CHG (SD)
Dryness	Base	47		91	
	Week 2	44	-.93 (0.90)	87	-1.1 (1.03)
	Week 7	44	-.84 (1.16)	84	-1.4 (1.01)
	Week 12	38	-.89 (1.25)	79	-1.5 (0.89)
Dyspareunia	Base	40		70	
	Week 2	30	-.77 (1.01)	51	-.90 (1.17)
	Week 7	30	-.97 (1.27)	56	-1.6 (1.11)
	Week 12	27	-.96 (1.19)	51	-1.7 (0.97)
Irritation	Base	47		91	
	Week 2	44	-.50 (1.00)	87	-.54 (1.02)
	Week 7	44	-.55 (1.30)	84	-.77 (0.97)
	Week 12	38	-.53 (1.41)	79	-.92 (0.94)
Soreness	Base	47		91	
	Week 2	44	-1.2 (0.95)	87	-1.3 (1.07)
	Week 7	44	-1.2 (1.15)	84	-1.7 (0.98)
	Week 12	38	-1.2 (1.26)	79	-1.8 (0.92)
Discharge	Base	47		91	
	Week 2	44	0.18 (0.76)	87	0.13 (0.71)
	Week 7	44	0.05 (0.71)	84	0.10 (0.80)
	Week 12	38	-.05 (0.84)	79	0.00 (0.73)

Strong placebo effects were noted at week 2 for all symptoms and were sustained, but less so, at weeks 7 and 12 as noted in Table 6.

Vaginal health was a secondary efficacy end point consisting of a composite score of secretions, epithelial integrity, epithelial surface thickness, color, and pH. The composite score over time showed statistically significant improvement ($p \leq 0.001$) for the Vagifem group compared with placebo at weeks 2,7, and 12.

Vaginal cytology was another secondary efficacy endpoint. Subjects receiving Vagifem had significantly increased percentages of superficial and intermediate cells, reflected in an increase in Maturation Value at week 2 ($p \leq 0.001$) and week 7 ($p=0.008$, LOCF analysis), but not at week 12,

probably because the maximal degree of proliferation had been achieved after week 7, but before week 12. The Maturation Value was, however, mathematically higher at week 12 for Vagifem than for placebo. Maturation Values for placebo rose from a mean of 46.2 at baseline to 53.0 at week 2, 55.7 at week 7, and 54.3 at week 12. Maturation Values for Vagifem rose from a mean of 47.4 at baseline to 66.8 at week 2, 63.9 at week 7 and 59.7 at week 12.

Urethral cytology was a third secondary efficacy endpoint. Results were somewhat similar to those for vaginal cytology. There was a shift over time from immature basal cells to the more mature intermediate a1nd superficial cells. Subset analyses for age (≤ 65 and 76.5 years), hysterectomy status (yes and no), duration of postmenopause (0-5 years, 5-10 years, and ≥ 10 years), and subjects with moderate/severe dryness and soreness at baseline were consistent with those found in the total population for relief of vaginal symptoms.

b. Safety:

Endometrial biopsies were done on 32 Vagifem subjects and 21 placebo subjects at the end of 12 weeks of treatment (Table 7). Three subjects in each group had insufficient tissue collected. The other 18 subjects in the placebo group had atrophic endometrium and 27 subjects in the Vagifem group had atrophic endometrium. (One of three pathologists read Vagifem subjects 116 and 193 as "proliferative" endometrium, but the other two pathologists read the biopsies as atrophic endometrium and they were listed as such.) Vagifem subject 257 had proliferative endometrium at 12 weeks and Vagifem subject 179 had simple hyperplasia at 12 weeks of treatment. This subject had a repeat biopsy 2 1/2 months later which was reported as proliferative endometrium which had resolved spontaneously.

Table 7

Endometrial Biopsy Results Comparing Vagifem with Placebo After 12 Weeks of Treatment

	Vagifem	Placebo
Total number of subjects Randomized	91	47
Non hysterectomized subjects Randomized	49	24
Total Biopsies	32	21
Insufficient Tissue	3	3
Simple Hyperplasia	1*	0
Proliferative Endometrium	1	0
Weakly Proliferative	0	0
Atrophic Endometrium	27	18

* resolved spontaneously to proliferative endometrium 2 1/2 months later.

Adverse events most frequently reported (≥ 5%) were headache, back pain, genital moniliasis, upper respiratory infection, vaginitis, and vaginal discomfort as indicated in Table 8.

Table 8

Sponsor's Table 9.2.1

Treatment-Emergent Adverse Events:

Number of Adverse Events with Occurance Rates of ≥ 5%

Adverse Event	Placebo	Vagifem
Back pain	3 (6%)	6 (7%)
Headache	3 (6%)	8 (9%)
Abdominal pain	2 (4%)	6 (7%)
Vaginitis	3 (6%)	3 (3%)
Moniliasis genital	1 (2%)	5 (5%)
Upper respiratory infection	2 (4%)	5 (5%)

Most of the adverse events reported were mild or moderate in severity. One subject in the placebo group and 4 subjects in the Vagifem group discontinued study prematurely because of adverse events. The placebo subject discontinued because of hot flushes. One Vagifem subject discontinued because of agitation and insomnia. The other 3 Vagifem subjects discontinued because of renal carcinoma, moniliasis genital, and exacerbation of lichen, respectively. A placebo subject was found comatose in her

swimming pool, kept on life support for five weeks, and died.

No clinically significant shifts from normal to abnormal occurred in blood chemistries, hematology, or urinalyses during the clinical trial.

There was systemic absorption of estradiol as indicated by the estradiol levels listed below. Table 9 shows the serum estradiol levels at baseline and after 2, 7, and 12 weeks of treatment.

Table 9
Sponsor's Table 9.8
Serum Estradiol Levels - Mean ± SD (PG/ML)

Visit	Placebo	Vagifem
Baseline	11.8 ± 17.6	10.3 ± 21.5
Week 2	9.9 ± 16.9	31.3 ± 40.2
Week 7	8.3 ± 9.5	20.3 ± 37.5
Week 12	6.2 ± 2.9	18.7 ± 26.1

18. Reviewer's Comments:
Study 9/USA is a pivotal study for efficacy and safety over a 12 week treatment period. The inclusion and exclusion criteria are appropriate. The clinical trial demonstrated that Vagifem is effective in the relief of symptoms of postmenopausal, estrogen deficiency - derived atrophic vaginitis. Vagifem was more effective than placebo in the relief of symptoms of the dryness, soreness, and irritation associated with atrophic vaginitis based on the composite score of the three vaginal symptoms at weeks 7 and 12. Efficacy was maintained for individual symptoms for the 12 weeks of study. Although the efficacy effect of Vagifem was not strong compared with placebo, it was consistent across symptoms and in subgroup analyses.

The Maturation Value is an objective, biologic indicator of unequivocal stimulation of vaginal epithelium by estrogen. The Maturation Values obtained in this study indicate that Vagifem is more effective than placebo in producing an estrogen effect on the vaginal mucosa.

Serum estradiol levels indicate that there is some systemic absorption of estradiol from the vagina in at least some Vagifem subjects. However, the mean maximum rise of estradiol above baseline in Vagifem subjects was only 21 pg/mL, which occurred at week 2. This rise compares favorably with some of the smaller transdermal estrogen patches (Fempatch = 22 pg/mL above baseline; Vivelle = 25pg/mL above baseline).

No subject in the placebo group developed endometrial hyperplasia or proliferative endometrium. However, one subject in the Vagifem group developed simple endometrial hyperplasia and another developed proliferative endometrium indicating that there is some stimulation of the endometrium with the use of Vagifem. Only 32 of the 91 Vagifem-treated subjects had endometrial biopsies performed so we do not know how many additional subjects might have had some proliferative or hyperplastic changes. The one case of hyperplasia did resolve spontaneously to proliferative endometrium. While 49 Vagifem subjects had uteri, 17 of them did not have endometrial biopsies as required, nine because of a stenotic cervix, three because the investigator was unable to pass the Pipelle, and the others for a variety of individual reasons.

Treatment-emergent adverse reactions were usually mild or moderate in severity and not of an alarming nature.

Overall, Vagifem treatment is safe and effective for its indicated use.

B. Study 5/CAN: Vagifem vs Premarin Vaginal Cream - a Randomized, Open, Controlled, Parallel Study of Efficacy and Safety in Patients with Estrogen Deficiency - Derived Atrophic Vaginitis

1. Investigators and Sites:

Jacque - Emile Rioux	Ste - Foy, Quebec
Morrie Gelfand	Montreal, Quebec
Wilfred Steinberg	Toronto, Ontario
Marion Powell	Toronto, Ontario
M. Corinne Devlin	Hamilton, Ontario
Douglas Hepburn	Oshawa, Ontario

2. Objectives of the Study:
To assess the effect of Vagifem in comparison with Premarin Vaginal Cream regarding relief of postmenopausal estrogen deficiency-derived atrophic vaginitis, systemic absorption as determined from estradiol and FSH blood levels, vaginal cytology, and endometrial status.

3. Rationale for the Study:
With the decline in endogenous estrogen production during the menopause, the vagina (and other estrogen - dependent tissues) gradually undergo atrophic changes. The vaginal epithelium becomes thin and pale. The most effective treatment is either topical or systemic estrogen.

4. Method of Assignment to Treatment:
Subjects who fulfilled inclusion criteria after the 4-week run-in period were randomized to either Vagifem or Premarin Vaginal Cream (2 grams containing 625 micrograms per gram of conjugated equine estrogens) according to a 1:1 randomization scheme.

5. Numbers of Subjects:
One hundred sixty subjects were randomized; 159 were treated (80 Vagifem, 79 Premarin).

6. Duration of Clinical Trial:
After a 4-week run-in period without treatment, subjects entered a 24-week period of active treatment.

7. Inclusion Criteria:

— Subjects aged ≥ 40 and≤ 80 years of age

— Presence of at least two symptoms of estrogen deficiency-derived atrophic vaginitis (vaginal dryness, vaginal soreness, vaginal irritation, dyspareunia) classified by the subjects as moderate or severe

— Subjects with intact uteri

— At least one year of amenorrhea

- Serum estradiol ≤ 29.9 pg/ml (110 pmol/L)
- Vaginal smear showing at least 30% parabasal cells (subsequently deleted)
- Serum FSH ≥40 IU/L
- Willing to give written informed consent to participate in the study

8. Exclusion Criteria:

- Known, suspected, or past history of carcinoma of the breast
- Known or suspected estrogen-dependent neoplasia
- A positive or suspicious mammogram
- Subjects with systemic malignant diseases
- Abnormal genital bleeding of unknown etiology
- Acute thrombophlebitis, thromboembolic disorders, or a past history of these conditions associated with previous estrogen use
- Subjects treated with testosterone and estradiol in oil (Climacteron) within four months of study entry
- Subjects who have received medication for the treatment of atrophic vaginitis within three months of study entry
- Use of any type of vaginal preparation within 7 days of entry
- History of treatment with DES (diethylstilbestrol)
- Corticosteroid or sex hormones within three months of study entry
- Known or suspected allergy to the test drug or the

vaginal tablet constituents

— Exposure to any investigational drug within the past 30 days

— Subjects who are unwilling to agree to the provisions of the protocol

— Pregnancy

9. Trial Period: April 23, 1993 through January 29, 1995

10. Dose and Mode of Administration:
Subjects in the Vagifem group inserted one Vagifem tablet intravaginally daily for 2 weeks, then one Vagifem tablet twice weekly for the following 22 weeks. Subjects in the Premarin group inserted Premarin Vaginal Cream 2 grams intravaginally, containing 1.25 mg of conjugated estrogens, daily for 3 weeks, withheld application for one week, and then repeated the regimen for a total of 24 weeks. (The recommended dosage of Premarin Vaginal Cream in 1999 is 1/2 to 2 grams per application, so this study employed the maximal approved dose of Premarin Vaginal Cream).

11. Efficacy Assessments:
The primary efficacy variable was relief of vaginal symptoms (vaginal dryness, soreness, and irritation) from baseline to week 12 (although week 24 was also evaluated) based on the change in the composite score, last observation carried forward. For each primary efficacy symptom, numerical scores of 0, 1, 2, and 3 were assigned to none, mild, moderate, and severe, respectively. The composite score was calculated as the average of the scores for vaginal dryness, soreness, and irritation. Vaginal cytology-and evaluations of estradiol and FSH were secondary efficacy variables.

12. Safety Assessments:
Adverse events observed by the subjects or investigators were recorded and evaluated. C.B.C.s, blood chemistries, urinalyses, and results of pregnancy tests were recorded and evaluated. Endometrial biopsies were collected with either the[samplers. Pap smear results were also recorded and evaluated. Evaluation of endometrial biopsies were made by two independent pathologists, blinded to treatment group and each other's interpretation.

13. Disposition of Subjects:

One hundred fifty-nine subjects were treated. The number of subjects at each investigational site is shown in Table 10.

Table 10
Sponsor's Table 1
Number of Treated Subjects by Investigator

Investigator	Vagifem	Premarin	Total
Rioux	18	18	36
Gilfand	18	16	34
Steinberg	5	5	10
Powell	6	6	12
Devlin	33	33	66
Hepburn	0	1	1
Total No. of Subjects	80	79	159

Of the 159 subjects treated, 126 completed the study according to the protocol. The study completion status and percentage of subjects who did not complete the study are shown in Table 11. Three times as many Premarin subjects as Vagifem subjects did not complete the study.

Table 11
Sponsor's Table 2
Study Completion Status

	Vagifem	Premarin
No. Of Subjects Treated	80 (100%)	79 (100%)
Completed Study	72 (90%)	54 (68%)
Reason for Not Completing		
Adverse Event	4 (5%)	14 (18%)
Non-compliance	2 (3%)	8 (10%)
Other	2 (3%)	3 (4%)
Total Non-completions	8 (10%)	25 (32%)

Seven of the Premarin discontinuations were investigator initiated and two of the Vagifem discontinuations were investigator initiated.

14. Protocol Deviations:
Vagifem subject 104 and Premarin subject 126 were discontinued because of excessive estradiol levels at entry. Most protocol deviations were minor and scattered among the sites and treatment groups.

15. Demographic and Background Features:
Subjects were similar in both treatment arms for vaginal appearance and symptoms.

Table 12 summarizes subject demographic and background information. The mean age was 57.3 years. The mean weights were 64kg for Vagifem subjects and 69 kg for Premarin subjects.

Table 12
Sponsor's Table 4
Demography and Background Features

	Vagifem	Premarin
Total Subjects Treated	80	79
Age (years)		
Mean (SD)	57.3 (7.1)	57.2 (7.8)
Min-Max	45.0-76.0	42.0 - 85.0
Race (n, %)		
White	77 (96%)	77 (97%)
Non-White	3 (4%)	2 (3%)
Weight (kg)		
Mean (SD)	64.4% (9.0)	69.3 (13.4)
Min-Max	49.4-88.1	46.5-100.0
Years since last mensus		
Mean (SD)	7.9 (7.0)	7.6 (7.2)
Min-Max	1.0-36.9	1.0-30.7
Superficial cells (%)		
Mean (SD)	3.4 (5.7)	2.9 (5.0)
Min-Max	0-25	0-25
Parabasal cells (%)		
Mean (SD)	40.3 (44.5)	31.1 (39.7)
Min-Max	0-100	0-100

16. Extent of Exposure:
The number of subjects with at least 80% compliance completing specified time periods is shown in Table 13, Eleven percent of Vagifem subjects and 32% of Premarin subjects with at least 80% compliance did not complete study.

Table 13
Sponsor's Table 16
Number of Subjects at Each Visit (≥ 80% Compliance)

Week	Vagifem	Premarin	Total
0	80	79	159
2	78	70	148
12	72	59	131
24	71	54	125

17. Results:

a. Efficacy:
The analysis of the composite score for vaginal symptoms at week 12, the primary efficacy endpoint, demonstrated that Vagifem tablets and Premarin Vaginal Cream are equivalent in efficacy and provide similar relief of symptoms. Table 14 summarizes the results from the primary analysis for this study. The upper limit of the 95% CI is 0.08, which is smaller than the pre-specified value. Thus it can be concluded that Vagifem is equivalent to Premarin in efficacy. Among centers, the change from baseline in composite symptom scores at week 12 was consistent except for the two smallest centers where there was a smaller decrease in the Premarin group.

Table 14
(Sponsor's Table 7.2)
Relief of Symptoms - Mean Change in Composite Score of Three Symptoms at Week 12 (LOCF)

Treatment	N	Baseline	Week 12	Change (SE)	Treatment Comparison 95% CI	P-value
Premarin	80	1.63	0.63	-1.00 (0.09)	(-0.40, 0.08)	0.218
Vagifem	80	1.68	0.52	-1.16 (0.09)		

Vaginal cytology was a secondary efficacy endpoint. Mean values for parabasal cells decreased significantly from screening to end of study in the Vagifem and Premarin groups with no difference between groups. No correlation can be made among the parabasal cell results and the subject's evaluation of vaginal symptoms and the investigator's evaluation of vaginal atrophy.

The combination of intermediate plus superficial cells at week 12 was 99.07% for Vagifem and 97.45% for Premarin and at week 24 was 95.89% for Vagifem and 99.17% for Premarin. Assessment of vaginal cytology indicated significant increases in the Maturation Value for both drugs. During the maintenance period, Maturation Values for subjects in both treatment arms remained significantly improved compared with baseline. The mean Maturation Value decreased slightly with time in the Vagifem treatment arm. By week 24, Maturation Values for the Premarin treatment arm were statistically significantly higher than for the Vagifem treatment arm.

Estradiol and FSH levels were also secondary efficacy endpoints. Levels of estradiol and FSH outside of the postmenopausal ranges occurred infrequently with Vagifem as compared with Premarin. At week 2, 9% of Vagifem subjects and 73% of Premarin subjects had estradiol levels higher than the postmenopausal range. At week 12, 3% of Vagifem subjects and 43% of Premarin subjects had estradiol levels above the postmenopausal range. At week 24, 5% of Vagifem subjects and 47% of Premarin subjects had estradiol levels above the postmenopausal range.

b. Safety:

Endometrial biopsies were performed on 49 Vagifem subjects and 49 Premarin subjects at the end of treatment. The results are shown in Table 15.

Table 15
Sponsor's Table 9.7
Endometrial Biopsy Results at Week 24

	Vagifem	Premarin
Total Subjects Enrolled	80	79
Total Biopsies	49	49
Insufficient Tissue	14 (28%)	21 (42%)
Complex Hyperplasia	0 (0%)	1 (2%)
Simple Hyperplasia	0 (0%)	1 (2%)
Proliferative Endometrium	1 (2%)	7 (14%)
Weakly Proliferative	0 (0%)	4 (8%)
Atrophic Endometrium	34 (68%)	15 (30%)

Adverse events most frequently reported (≥ 5%) were upper respiratory tract infection, headache, and pruritis genital for Vagifem subjects and postmenopausal bleeding, breast pain, perineal pain, upper respiratory tract infection, pruritus genital, headache, abdominal pain, flatulence, and influenza-like symptoms for Premarin subjects as indicated in Table 16. Two Vagifem subjects had severe adverse events (allergic reaction and stroke) and 10 Premarin subjects had severe reactions. One of the Vagifem subjects with a severe reaction and 8 of the Premarin subjects with severe reactions had the drug discontinued.

The Vagifem subject with the allergic reaction had been using Vagifem for 165 days before the reaction occurred. It was considered unlikely to be related to Vagifem and the subject continued on Vagifem treatment.

The Vagifem subject with the stroke had been using Vagifem for 65 days. The stroke was recorded by the investigator as having an unlikely relationship to Vagifem. The drug was discontinued and the subject was hospitalized for seven days.

Four of the severe Premarin reactions were probably related to the drug. These reactions were vaginitis,

pruritis genital, and perineal pain, all of which occured 4-6 days after starting therapy, and uterine bleeding which occurred in a subject after 95 days of therapy.

Four of the severe Premarin reactions were possibly related to the drug. These reactions were migraine, hypertension, depression, and urinary tract infection.

One of the severe Premarin reactions was unlikely to be related to the drug. This was a case of cystitis and frequent micturition.

The realtionship of headache occuring in a Premarin subject after 64 days of therapy to the drug was reported as unknown.

Table 16
(Sponsor's Table 15)
Treatment-Emergent Adverse Events:
Number of Adverse Events with Occurrence Rates of ≥ 5%

Adverse Event	Vagifem	Premarin
Pruritus genital	5 (6%)	5 (6%)
Headache	8 (10%)	4 (5%)
Abdominal pain	3 (4%)	4 (5%)
Flatulence	0 (0%)	4 (5%)
Upper respiratory infection	9 (11%)	4 (5%)
Breast pain	0 (0%)	7 (9%)
Perineal pain	0 (0%)	6 (8%)
Postmenopausal bleeding	2 (3%)	13 (16%)
Influenza-like	2 (3%)	4 (5%)

Most of the adverse events reported were mild or moderate in severity.

Changes in mean blood chemistry and hematology from screening to end of treatment were within the reference ranges and not clinically significant. Individual changes from normal to abnormal were few and did not require

medical management.

c. Study Drug Acceptance:
Subjects were asked about treatment acceptability through personal and telephone interviews conducted during weeks 2, 5-6, 12, 17-19 and 24 of the clinical trial. By the end of treatment, the majority of Vagifem subjects (93%) found drug administration easy compared with 66% of Premarin subjects; 92% found Vagifem comfortable to use versus 50% of Premarin subjects; and 77% found Vagifem treatment very acceptable overall versus 25% of Premarin subjects.

18. Reviewer's Comments
Study 5/CAN is the second pivotal clinical trial for efficacy and safety. The treatment period extended for 24 weeks. The trial was an active comparison of Vagifem and Premarin Vaginal Cream. The inclusion and exclusion criteria were appropriate. Many more Premarin users than Vagifem users dropped out and did not complete the study. This substantial difference in discontinuation rates (32% for Premarin and only 10% for Vagifem) could bias the comparisons in efficacy between the two active treatment arms. The fact that the study was unblinded also could compound the biased comparisons in efficacy between the Premarin and Vagifem treatment arms. This tends to somewhat weaken the conclusion that the clinical trial demonstrated that Vagifem is equivalent to Premarin in relief of symptoms of atrophic vaginitis based on the composite score of three vaginal symptoms (dryness, soreness, and irritation) at week 12. The treatment effect of both Vagifem and Premarin began after two weeks and was maintained over time, with no significant difference between the treatments.

Vaginal cytology indicated significant increases in the maturation value for both Vagifem and Premarin.

Serum estradiol levels above the postmenopausal range and FSH levels below the postmenopausal range, although infrequently occurring in Vagifem subjects, indicate that there is sometimes systemic absorption of estradiol from the vagina.

Only 49 of 80 Vagifem subjects and 49 of 79 Premarin subjects had

endometrial biopsies at the end of treatment. One Vagifem subject developed proliferative endometrium indicating stimulation of the endometrium. There was considerable greater stimulation of the endometrium in the Premarin subjects. We do not know how many of the other subjects who did not have endometrial biopsies would have developed proliferative or hyperplastic changes.

Treatment - emergent adverse reactions were usually mild or moderate in severity and not of an alarming nature. The two severe reactions that did occur in Vagifem subjects (allergic reaction; stroke) were unlikely related to the drug. Overall, Vagifem treatment is safe and effective for its indicated use.
The interviews conducted during the clinical trial asking about treatment acceptability indicated that Vagifem was very acceptable to use.

C. Study 33/ATR. Supportive Efficacy and Safety Trial

Study 33/ATR was conducted in Denmark form May 12, 1989 through April 19, 1990. Subjects were 45-70 years of age with symptoms due to atrophic vaginitis including dryness, soreness, irritation, dyspareunia, and discharge. Subjects could not have received estrogen treatment within one month prior to study entry. The primary objective of this study was to evaluate investigator assessed changes in vaginal atrophy during the treatment period of Vagifem in comparison with placebo. Secondary objectives were to calculate the incidence of subjective symptoms due to atrophic vaginitis.

This double-blind, multicenter (25 centers), placebo-controlled, parallel group study was designed to evaluate and compare the efficacy of Vagifem treatment and placebo in relieving symptoms from atrophic vaginitis due to estrogen deficiency in the postmenopause. After a 4 week period without any oral or local estrogen treatment 164 patients were treated, 81 on Vagifem treatment and 83 on placebo treatment. The patients received 1 vaginal tablet each day the first 2 weeks followed by a twice weekly administration of 10 weeks.

The study included 3 visits; visit 1 start of treatment, visit 2 after 2 weeks of treatment, and visit 3 after 12 weeks of treatment. At each visit the investigators assessed the grade of vaginal atrophy by inspection. The primary efficacy parameter was defined as none or mild vaginal atrophy. The patients registered their subjective symptoms as dryness, soreness, irritation, dyspareunia and vaginal discharge.

Of the 81 patients receiving Vagifem 6 dropped-out compared to 4 drop-outs of the 83 on placebo treatment, one from each group due to lack of treatment effect. The duration of treatment of the dropouts is unknown. Baseline comparison of treatment groups was performed on the basis of all patients treated (164). No statistical significant difference was found between the two treatment groups.

Efficacy parameters were analyzed by comparing the 2 treatment groups at each visit. At baseline 21.0% in the Vagifem group and 16.9% in the placebo group had none or mild atrophy. At visit 2 (after 2 weeks treatment) a high statistical significant treatment effect of Vagifem (87.0%) compared to placebo (64.2%) was found. At visit 3 (week 12) this treatment effect was still highly statistically significant, for Vagifem 89.7% and for placebo 69.5%. Analyzing different subsets of patients (including or not drop out, protocol violators etc.) did not change this picture. The subjective symptoms of dryness, soreness, irritation and dyspareunia also shows a statistical significant treatment effect in favor of Vagifem at week 12.

No patients in either group reported serious adverse events. Twelve in the Vagifem and 15 in the placebo group reported adverse events. In the Vagifem group adverse events included not unexpected events such as slight vaginal bleeding, skin rash and vaginal discharge.

Seventy nine percent of the patients found the applicator convenient to use. The results of this study support the effect of Vagifem compared to placebo treatment on vaginal atrophy and the subjective symptoms related to vaginal atrophy.

Reviewer's Comments:
The duration of treatment for each subject was not available. While study 33/ATR does support the efficacy and safety of Vagifem over a 12 week treatment period it is noted that this study was actually conducted before the two pivotal clinical trials and that the primary efficacy endpoint of study 33/ATR was the investigator's assessment visually of the severity of the atrophic vaginitis at baseline and at the end of 2 and 12 weeks of therapy while the primary efficacy endpoints of the pivotal trials were the subject's assessment of vaginal symptoms at pertinent time points. In study 33/ATR, the subject's assessment of vaginal symptoms was a secondary endpoint. Also, evaluable data were not well documented. Revisions of data were not always initialed and dated.

D. Study 12/USA, An Open-Label, Multi-center Study Evaluating Safety and Efficacy of Vagifem 25 micrograms During Long-Term Treatment of Estrogen Deficiency-Derived Atrophic Vaginitis: An Extension Study to VAG/9.

The objective of this study was to assess the safety and efficacy of Vagifem for an additional 52 weeks in postmenopausal subjects who were previously enrolled in study 9/USA, a 12 week study. Upon successful completion of study 9/USA, all 195 completing subjects were given the option to either continue Vagifem twice weekly from the preceding trial, switch to Vagifem from placebo or estradiol, 10 micrograms, or not to enter into the new trial. The subset of study 9/USA who elected to continue in the extension trial were entered into study 12/USA.

The investigators were the same as those in study 9/USA except for Dr. Rogerio Lobo. The primary objective of this study was to evaluate the long-term safety of Vagifem on the endometrium and the secondary objective was to evaluate the efficacy of Vagifem for an additional 52 weeks. Due to the nature of the study design, subjects were categorized into three groups, based on the medications they received in study 9/USA:

	Treatment Received	
Group	9/USA	12/USA
1	Placebo	Vagifem
2	Estradiol, 10 μg	Vagifem
3	Vagifem	Vagifem

There were no notable differences between the groups for any demographic or baseline variables. Inclusion and exclusion criteria were the same as these for study 9/USA. A total of 102 subjects were treated with Vagifem in this study, 38 of whom had also been treated with Vagifem in study 9/USA. A total of 76 subjects completed the full 52 weeks of study. The mean composite scores of vaginal symptoms (dryness, soreness, and irritation) at week 52 were comparable for all three groups: 0.43 for Placebo/Vagifem, 0.28 for E_2 10μg/Vagifem and 0.36 for Vagifem/Vagifem. All three groups showed statistically significant reductions from baseline to week 52 in the change in composite score over time.

Vaginal cytology showed maintenance of Maturation Values in all groups throughout this extension study.

The most frequently occurring treatment-emergent adverse events (U.R.I., genital moniliasis, headache, vaginitis, sinusitis, influenza-like symptoms, and abdominal pain) were generally mild or moderate in severity. Except for genital moniliasis and breast pain, which were probably or possibly related to study drug, these events were not considered related to study drug.

Evaluation of endometrial biopsies was performed for 42 subjects, most of them at baseline and repeated at the end of 52 weeks. Three of them were performed only at 52 weeks and five of them were done only at baseline and not at the end of the study. Twelve subjects had insufficient tissue for a histological classification. One subject had findings of note. Subject 041 had received estradiol 10 micrograms during study 9/USA and had atrophic endometrium at 12 weeks when she entered study 12/USA and began using Vagifem. She had proliferative endometrium at the end of 52 weeks. Serum estradiol levels of subjects in this study suggested that there is minimal systemic absorption of estradiol from the vagina.

Reviewer's Comments:
Most subjects in the study did not have endometrial biopsies. We do not know how many of these subjects might have developed proliferative or hyperplastic changes. The fact that subject 041 developed proliferative endometrium while using Vagifem indicates that Vagifem can and sometimes does stimulate the endometrium. This is not surprising given the fact that serum estradiol levels showed that there is some absorption of estradiol from the vagina.

Treatment-emergent adverse events reported were usually mild or moderate in severity and unlikely to be directly related to the use of Vagifem.

Vagifem was effective for the long-term treatment of atrophic vaginitis. Relief of vaginal symptoms was maintained through 52 weeks of treatment.

E. Study 6/CAN. An open Study to Assess the Continuing Safety and Efficacy of Vagifem in the Treatment of Atrophic Vaginitis in Patients Who Have Completed 5/CAN and are Continuing on Vagifem.
The objective of this study was to assess the safety and efficacy of Vagifem for an additional treatment period of 28 weeks in postmenopausal subjects who were previously enrolled in study 5/CAN, a 24 week active treatment study. Out of 126 subjects who successfully completed study 5/CAN, 56 elected the option to continue on Vagifem in study 6/CAN. The

investigators were the same as for study 5/CAN. The inclusion and exclusion criteria were the same as for study 5/CAN. Vagifem, 25 microgram tablets, were inserted twice weekly into the vagina. A total of 37 subjects continued on Vagifem therapy from study 5/CAN and 19 subjects switched from Premarin in study 5/CAN to Vagifem in study 6/CAN. A total of 32 (85%) subjects in the Vagifem/Vagifem group and 16 (84%) subjects in the Premarin/Vagifem group completed the study. There were no notable differences between the groups for any demographic or baseline variables.

Statistically significant improvement from baseline in the relief of vaginal symptoms (mean score of dryness, soreness, and irritation) were shown within both groups at weeks 38 and 52.

Vaginal cytology showed maintenance of Maturation Values in both groups from week 24 to week 52.

Most treatment-emergent adverse events were mild or moderate in severity.

End-of-treatment biopsy results were available in 20 Vagifem/Vagifem subjects and 16 Premarin/Vagifem subjects at the end of 52 weeks. Fourteen of the Vagifem/Vagifem subjects had atrophic endometrium and 6 subjects had insufficient tissue. Nine of the Premarin/Vagifem subjects had atrophic endometrium, 6 subjects had insufficient tissue, and 1 subject had weakly proliferative endometrium.

An elevated serum estradiol level was found in only one subject. In the Vagifem/Vagifem group, one subject had a serum estradiol level of 204 pmol/L at week 38.

Reviewer's Comments:
Twenty of the 56 subjects enrolled did not have end-of-treatment endometrial biopsies done so we do not know how many of these subjects would have developed proliferative or hyperplastic endometrial changes. The one subject who did develop weakly proliferative endometrium indicates that Vagifem can and sometimes does stimulate the endometrium. Elevated serum estradiol levels were not a problem in this study. No new or unexpected safety findings were identified. Relief of vaginal symptoms was maintained through week 52.

F. Study 7/END. Local Treatment of Estrogen Deficiency Derived Atrophic Vaginitis with Two Dosage Regimens of Low-dose Estradiol Vagitories - Vagifem. Systemic Influence and Efficacy.

The objective of this study was to evaluate the efficacy of two different maintenance doses of Vagifem on estrogen deficiency derived atrophic vaginitis in postmenopausal women and to obtain safety data on the endometrium during the treatment. It was an open, comparative study where the subjects were treated with daily vaginal applications of Vagifem for 2 weeks followed by allocation to either once or twice weekly maintenance therapy regimen for 50 weeks. A total of 51 postmenopausal women were recruited. The first 34 subjects were allocated to the twice weekly maintenance therapy regimen and the last 17 subjects received the once weekly maintenance therapy. Three subjects in each group dropped out, leaving 45 subjects completing the full 52 weeks of therapy. Subjects in the twice weekly maintenance group had almost complete relief of symptoms and normalization of the vaginal mucosa. The majority of subjects in the once weekly maintenance group continued to complain of mild symptoms. Thirteen subjects in the once weekly maintenance group had an atrophic endometrium and 1 had a weakly proliferative endometrium after 1 year of treatment. Twenty-nine subjects in the twice weekly maintenance group had an atrophic endometrium and two had a weakly proliferative endometrium after one year of treatment.

Reviewer's Comments:

This study is flawed by the fact that it was not a randomized study. It does, however, indicate that a twice weekly maintenance regimen of therapy may be the optimum dosage schedule for the relief of vaginal symptoms and gives more relief than a once weekly maintenance dosage schedule. It also indicates that weakly proliferative changes can occur in the endometrium of subjects receiving once or twice weekly maintenance dosages.

IX. Postmarketing Clinical Studies:
No postmarketing clinical trials are required.

X. Labeling Review:
Revised draft labeling dated March 19, 1999 which was submitted March 23, 1999 is satisfactory.

XI. Safety Update:
A 120 day safety report was submitted October 21, 1998. The report covers the

period April 1, 1998—September 26, 1998. During this period there were no spontaneously reported adverse events associated with Vagifem. There are no ongoing clinical trials for which additional safety data can be obtained.

A safety update of adverse events for Vagifem reported September 29, 1998 through February 25, 1999 was submitted March 1, 1999. Dysaesthesia was the only spontaneously reported adverse event associated with Vagifem.

XII. Reviewer's Overall Evaluation and Conclusions:

Vagifem is a low-dose estrogen vaginal tablet containing 25 micrograms of 17β-estradiol indicated for the treatment of atrophic vaginitis associated with estrogen deficiency related to the menopause. Topical or oral estrogen is generally recognized as being effective for the treatment of atrophic vaginitis. The applicant developed Vagifem specifically to treat atrophic vaginitis with the expectation that only minimal amounts of estradiol would be absorbed from the vagina and that it would be insufficient for treating vasomotor symptoms.

Six efficacy and safety clinical trials provided the bulk of the evaluable data in this application. A total of 369 subjects received Vagifem at the recommended dosage. Studies 9/USA and 5/CAN were the pivotal adequate and well-controlled studies. A total of 171 subjects were treated with Vagifem in these two clinical trials. Subjects were 40 to 85 years of age. The completion rate for Vagifem subjects in both studies was 90%.

Study 9/USA was a 12-week clinical trial designed to evaluate Vagifem compared with placebo. Vagifem resulted in a statistically-significant reduction in vaginal symptomalolgy which was apparent within two weeks of treatment and was sustained over 12 weeks. Although a statistically significant benefit was noted, the clinical relevance of this finding is less clear due to the strong placebo effect. The internal consistency of the subtle but significant effect of Vagifem, along with its favorable safety profile, however, support its approval. Finally, the biologic effects of Vagifem on the vaginal epithelium were clearly different from placebo. This also supports the efficacy of Vagifem over placebo from a biologic "mechanism of action" perspective. The long-term extension of this clinical trial (study 12/USA) demonstrated that this efficacy was maintained by the twice-weekly application of Vagifem for one year.

Study 5/CAN was a 24-week clinical trial comparing Vagifem with Premarin Vaginal Cream, a marketed active comparator which is approved by the FDA for treatment of atrophic vaginitis. Following 24 weeks of therapy, Vagifem and Premarin Vaginal Cream were equally effective, with both groups of subjects showing improvement in vaginal symptoms (soreness, dryness, and dyspareunia)

from baseline. The rates of response were equally rapid with both treatments. This clinical trial demonstrated that Vagifem was as effective as Premarin Vaginal Cream for the treatment of atrophic vaginitis. Regarding safety, the trial demonstrated that Vagifem was tolerated at least as well as Premarin Vaginal Cream, if not better, although the trial was not designed with this claim in mind. The completion rate for Vagifem subjects was 90% and only 68% for Premarin Vaginal Cream subjects.

Study 33/ATR was a 12-week, double-blind, placebo-controlled clinical trial which differed from the two pivotal trials in the primary objective of the study. In the two pivotal trials, the primary efficacy variable was the relief of vaginal symptoms based on the subject's evaluation. In study 33/ATR, the primary efficacy variable was the investigator's assessment of vaginal atrophy by inspection. The subject's assessment of vaginal symptoms was a secondary efficacy endpoint. Evaluable data were not well documented, but overall the clinical trial does support the efficacy of Vagifem for the treatment of atrophic vaginitis. The completion rate for Vagifem subjects was 93%.

Study 7/END was an open, parallel group, 52-week clinical trial designed to evaluate the efficacy of Vagifem in weekly versus twice-weekly doses for the maintenance of symptom relief. The study was not a randomized trial, but the results did support the twice weekly maintenance dose as being effective for relief of symptoms.

Studies 12/USA and 6/CAN were designed to assess the long-term safety and efficacy of Vagifem. Study 12/USA was an open-label 52-week trial while study 6/CAN was an open-label 28-week study. The studies were extensions of the two pivotal studies. All subjects in both extension studies received only Vagifem. Both extension studies demonstrated that Vagifem was safe and effective for the long-term treatment of atrophic vaginitis.

Vaginal cytology was a secondary efficacy endpoint in both pivotal studies. Study 9/USA demonstrated that Vagifem was more effective than placebo in promoting the maturation of vaginal mucosal cells at weeks 2 and 7, but not at week 12. Study 5/CAN demonstrated that the effects of Vagifem were comparable to Premarin Vaginal Cream after two weeks of daily treatment. The mean maturation value decreased slightly with time in the Vagifem group. By week 24, maturation values for the Premarin group were significantly higher than in the Vagifem group.

Most of the subjects (85%) in both pivotal studies were 65 years old or less. There was no evidence that subjects older than 65 years responded differently to

Vagifem treatment than younger women.

Race-drug interactions could not be assessed since 97% of subjects in study 9/USA and 98% of subjects in study 5/CAN were white.

No unexpected adverse events were reported. There was not an unusually high incidence of known and expected adverse events reported. The overall safety profile of Vagifem is favorable. In study 9/USA, adverse events led to discontinuation in 4% of Vagifem subjects and 2% of placebo subjects. No pattern of adverse events was seen and almost all of the adverse events that did occur were mild to moderate in severity. In study 5/CAN, a greater number of both severe and serious adverse events were reported in the Premarin Vaginal Cream group. There were 2 serious adverse events among Vagifem subjects and four among Premarin subjects. Adverse events occurring in study 5/CAN led to discontinuations in 18% of Premarin subjects and 5% of Vagifem subjects. Total discontinuation rates were 32% in Premarin subjects and 10% in Vagifem subjects, a substantial difference in rates.

The critical safety issue with Vagifem relates to the extent of systemic exposure to estrogen. In comparison with Premarin Vaginal Cream, the systemic absorption of estrogen is much lower after administration of Vagifem. In study 5/CAN, after 24 weeks of treatment, 47% of Premarin subjects and 5% of Vagifem subjects had serum levels of estradiol above the postmenopausal limit. The importance of this extent of systemic absorption is reflected in endometrial response. In study 9/USA, only 32 of the 91 Vagifem-treated subjects had endometrial biopsies at the end of the study. One Vagifem subject developed endometrial hyperplasia and another developed a proliferative endometrium indicating that there is some stimulation of the endometrium occurring with the administration of Vagifem. No subject in the placebo group developed proliferative endometrium or endometrial hyperplasia. The two Vagifem subjects exhibiting stimulation of the endometrium represent 6% of the biopsies performed in Vagifem subjects. Only 49 of 89 Vagifem subjects in study 5/CAN had endometrial biopsies at the end of treatment. One Vagifem subject developed a proliferative endometrium, again indicating stimulation of the endometrium. It is noted also that one subject who received estradiol, 10 micrograms during study 9/USA had atrophic endometrium at the end of 12 weeks when she entered study 12/USA and began using Vagifem. She had developed proliferative endometrium by the end of 52 weeks. Also, one subject in study 6/CAN developed weakly proliferative endometrium, again demonstrating that Vagifem can stimulate the endometrium.

Vagifem has been approved for marketing in 53 countries since 1990. Over 49 million doses have been distributed. A total of 20 serious adverse events have

been reported either through the postmarketing surveillance system or from other clinical trials not included in this application. It is unlikely that 14 of these adverse events are directly related to Vagifem administration. The other 6 serious adverse events may well be directly related to Vagifem administration. There are two reports of malignant endometrial neoplasms and 2 reports of endometrial hyperplasia. The other two reports are directly related to the use of the supplied applicator which is used to insert the Vagifem tablet. In one instance the patient ruptured her vaginal fornix. The other instance involved a patient who six weeks after a vaginal hysterectomy pushed the applicator through the sutures in the anterior vaginal wall.

Overall, it is concluded that Vagifem is safe and effective for the treatment of atrophic vaginitis.

XIII. Recommendation:
Approval of this application is recommended.

/S/

Ridgely C. Bennett, M.D., M.P.H.

/S/

Dep. Director HFD-580

NDA 20-908
VAGIFEM
Novo Nordisk Pharmaceuticals

Updated Safety review is included in the Medical Officer review dated 3-25-99.