
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Letter Date:	May 28, 1998
NDA:	20-908
Related dates	05/Jun/98, 22and 23/Oct/98, 27/Nov/98, 11/Dec/98, 19/Jan/99
Drug:	Vagifem®, estradiol controlled release vaginal tablet
Sponsor:	Novo Nordisk Pharmaceuticals Inc. (NNPI)
Indication:	Relief symptoms of atrophic vaginitis
Type of Submission,	Original NDA
Code:	3S (new formula, standard NDA)
Reviewer:	Soraya Madani, Ph.D. / Sam Haidar, R.Ph., Ph.D.

1 Synopsis

NDA 20-908 for Vagifem™ (25 µg estradiol vaginal tablet) was submitted on May 28, 1998 by Novo Nordisk Pharmaceuticals. It was amended on June 5, October 22 and 23, November 27, December 11, 1998; and on January 19, February 24 and March 4, 1999. The proposed therapeutic indication for Vagifem™ is the treatment of symptoms associated with atrophic vaginitis. The proposed therapeutic regimen is to administer Vagifem™ vaginally once daily for two weeks (initial dose), then administer Vagifem™ vaginally twice weekly (maintenance dose).

Vagifem™ is administered vaginally for local effects. This route of administration avoids hepatic and gastrointestinal first pass metabolism; therefore, a significantly smaller dose (relative to oral administration) can be used and lower systemic exposure is observed.

In support of NDA 20-908, the sponsor submitted two pivotal pharmacokinetic (PK) studies: Study 4/S, which evaluated the single dose and multiple dose pharmacokinetics of Vagifem™ over 14 days; and Study 10/USA, which evaluated the PK of Vagifem™ over 12 weeks.

2 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA-20-908, submitted on May 28, 1998 and its amendments, dated June 5, October 22 and 23, November 27, December 11, 1998; and January 19, February 24 and March 4, 1999. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewers have the following comments:

1. The proposed in vitro release specifications for estradiol are not acceptable, the recommended specifications are as follows:

Sampling Time

FDA Recommended
Specification

Sponsor's Proposed
Specification

2. Labeling should be modified as outlined in section 9.1, Labeling Comments, page 36.

Comments 1 and the recommendations should be communicated to the sponsor, as appropriate. Further clarification of the comments can be obtained by contacting the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II. Labeling comments are updated and communicated to the sponsor based on the last revised version submitted to FDA on March 4, 1999.

Soraya Madani, Ph.D. and Sam Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

IS/ 3/25/99
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RD initialed by Ameeta Parekh, Ph.D., Team Leader
FT signed by Ameeta Parekh, Ph.D., Team Leader

IS/ 3/25/99

cc:

NDA 20-908

HFD-870 (M. Chen, A. Parekh, S. Madani, S. Haidar)

HFD-580 (J. Mercier, R. Bennett)

CDR (Barbara Murphy for Drug)

Table of Contents

1	Synopsis	1
2	Recommendation	1
3	List of Abbreviations	4
4	Background	5
5	Formulation	6
6	In Vitro Drug Release	8
7	Analytical Methodology	15
8	Clinical Pharmacology and Biopharmaceutics	16
8.1	<i>Pharmacokinetics</i>	16
8.1.1	Single Dose and Multiple Dose	16
8.2	<i>Protein Binding</i>	19
8.3	<i>Bioavailability and Bioequivalence</i>	20
8.3.1	Absolute/Relative Bioavailability	20
8.3.2	Bioequivalence	20
8.3.3	Food Effect	20
8.3.4	Dose-Proportionality	20
8.4	<i>Special Population</i>	20
8.5	<i>Metabolism</i>	20
8.6	<i>Drug Interaction</i>	21
8.7	<i>Population Pharmacokinetics</i>	21
8.8	<i>PK-PD Relationship</i>	21
9	Proposed Labeling	22
9.1	<i>Labeling comments:</i>	36
	Attachments	41
	Attachment A.	42
	Attachment B.	47

3 List of Abbreviations

ADME	absorption, distribution, metabolism and/or elimination
AUC	area under the curve
C _{max}	maximum concentration
E ₁	estrone
E ₁ S	estrone sulfate
E ₂	17β-estradiol
ERT	estrogen replacement therapy
FSH	follicle stimulating hormone
HPMC	Hydroxypropylmethylcellulose
HRT	hormone replacement therapy
ICMA	Immunochemiluminescence Assay
PK	Pharmacokinetics
PD	Pharmacodynamics
LLQ	lower limit of quantification
N	number
NDA	new drug application
RIA	radio-immuno assay
SHBG	sex hormone binding globulin
t _{max}	time to maximum concentration
USA	United States of America

4 Background

(Volume 1)

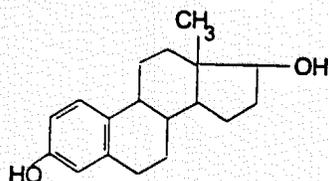
All women experience ovarian failure, usually between the ages of 45 and 55 years. This is characterized by marked decline, then cessation, of ovarian follicular activity and a consequent major decline of estrogen production, leading to decreased circulating estrogen levels and a permanent cessation of menstruation, i.e., menopause. The decline in circulating estrogen causes atrophic changes in the vaginal mucosa, which may result in symptoms of vaginal dryness, soreness, irritation, dyspareunia, and recurrent infections. Atrophic vaginitis requiring treatment often occurs in postmenopausal women who may neither need nor desire systemic estrogen replacement therapy (ERT) that may cause undesirable side effects.

Vagifem™ is a vaginal tablet containing 25 µg of estradiol (naturally occurring, 17-β-estradiol) supplied in disposable applicators. It is based on a hydrophilic cellulose derived matrix, offering controlled release of 17β-estradiol. The drug is used to treat the symptoms of atrophic vaginitis. The synthetically manufactured estrogen contained in Vagifem™ is chemically and biologically identical to the endogenous human estrogen (E₂), and is classified as a human estrogen. The rationale behind the development of Vagifem™ was to provide topical estrogen treatment for the effective relief of symptoms of atrophic vaginitis, without any of the undesirable effects associated with the systemic use of estrogens.

VAGIFEM™ (estradiol vaginal tablet) is a small, white, film-coated tablet containing 25.8 µg of estradiol hemihydrate equivalent to 25 µg of estradiol.

17β-estradiol hemihydrate is a white, almost white or colorless crystalline solid, chemically described as estra-1,3,5(10)-triene-3,17 diol. The chemical formula is C₁₈H₂₄O₂ · ½ H₂O with a molecular weight of 281.4.

The structural formula is:



The initial dosing regimen involves intravaginal administration of a single tablet each day for two weeks and maintenance dosing involves intravaginal administration of one tablet two times per week. Vagifem™ is currently marketed in 53 countries. However, two countries, France and Canada, refused the approval of the drug. The refusal in Canada was based on insufficient absorption data, the sponsor has conducted new studies and resubmitted the NDA to the Canadian Therapeutics Product. The refusal in France was due to changes in the European Pharmaceutical Approval Process.

The clinical development of Vagifem™ included seven studies conducted in the U.S. (3), Canada (2), Sweden (1), and Germany (1).

The pharmacokinetics (PK) data of Vagifem™ comes from two studies, 4/S and 10/USA. These studies contain information on single and multiple dose pharmacokinetics. In addition to the two PK trials, three pilot studies were conducted. These were not under the Sponsor's IND, and the case report form and full study reports are not available and are not a primary source of data.

The clinical studies also contained data on E₂ and E₁ and FSH serum/plasma levels at various times (up to 64 weeks).

Little is known about the pharmacokinetics and oral bioavailability of E₂ (estradiol). Most published data has measured total radioactivity, and therefore not discriminating between the parent drug and the metabolites. Findings to date suggest good oral absorption and high first-pass metabolism in the gut as well as liver, resulting in low bioavailability in humans. Once E₂ is in the systemic circulation, a fraction of it is excreted into the bile and then reabsorbed from the intestine (enterohepatic recycling).

Estrogen patterns of metabolism are different among the species. In human, the primary routes of metabolism are hydroxylation (16 α -OH and 2-OH metabolites) and conjugation with sulfate and glucuronic acid. Estradiol (E₂) is highly bound to the human plasma proteins (> 98%) and most of the radioactivity recovery has been observed in the urine.

Vagifem™, because of the topical vaginal application (locally) circumvents gastrointestinal and hepatic first-pass metabolism. Once E₂ reaches systemic circulation it gets metabolized to E₁ (estrone), estriol, and other estrogens.

5 Formulation

(Volume 13)

Vagifem®/™ tablet composition is summarized in the Table 1.

Table 1. Vagifem®/™ tablet composition.

Name of Ingredients	Quantity per Tablet	Function	Reference to Standards
Active ingredient: Estradiol hemihydrate ¹ equivalent to estradiol (anhydrous)	µg ² µg	Active Substance	USP ³ / NOVO ⁴
Inactive ingredients: Hypromellose ⁵ Lactose monohydrate Maize starch ⁷ Magnesium stearate	mg mg mg mg	Matrix former Filler Filler Lubricant	Ph. Eur. ⁶ Ph. Eur. Ph. Eur. Ph. Eur.
Film-Coating: (0.576 mg/tablet) Hypromellose Macrogol 6000 ⁸	mg mg	Film former Plasticizer	Ph. Eur. NF ⁹

¹ Estradiol hemihydrate Ph. Eur. = Estradiol USP

² Adjustment of water content is 3.2%

³ USP = United State Pharmacopeia

⁴ NOVO = Internal Standard

⁵ Hypromellose Ph. Eur. = HydroxypropylMethylcellulose USP

⁶ Ph. Eur. = The European Pharmacopeia

⁷ Starch NF

⁸ Polyethylene Glycol 6000 NF

⁹ NF = the National Formulary

The composition of the tablet formulation used in the pivotal clinical trials is the same as to be marketed formulation. An overview of the formulations used in the pivotal clinical trials and pharmacokinetics studies are described in this section (Table2).

In the pivotal clinical trials two strengths of Vagifem tablets were used, 25 and 10 µg estradiol, in addition to the placebo tablets. The formulations of the two strength tablets were identical except for the estradiol content.

In the two main pharmacokinetic studies (4/S, 10/USA) vaginal 10 µg E₂ (estradiol) tablet non-commercial formulation was included as a low dose comparison with Vagifem.

Table2. Summary of the formulation and batches used in the pharmacokinetics and pivotal clinical trials.

TRIAL	BATCH #	DATE OF manufacture	PLACE OF MANUFACTURE	LOT # Estradiol	SUPPLIER Estradiol	BATCH Size
Pivotal Clinical						
5/CAN						
25 µg Vagifem	1296-05	23-Oct-91	SDF Production 5A, Bagsvaerd	028309		kg
25 µg Vagifem	2179-04	27-Jun-92	SDF Production 5A, Bagsvaerd	028309		kg
25 µg Vagifem	3208-051	27-Jul-93	SDF Production 5A, Bagsvaerd	319324		kg
9/USA						
25 µg Vagifem	406355	14-Feb-94	SDF Production 5A, Bagsvaerd	333303		kg
10 µg Vagifem	404257	14-Feb-94	SDF Production 5A, Bagsvaerd	333303		kg
Placebo	404256	14-Feb-94	SDF Production 5A, Bagsvaerd	-		kg
PK studies						
10/USA						
25 µg Vagifem	406355	14-Feb-94	SDF Production 5A, Bagsvaerd	333303		kg
10 µg E ₂	404257	14-Feb-94	SDF Production 5A, Bagsvaerd	333303		kg
4/S (006/ABS)						
25 µg Vagifem	811871	Apr.88	Pharm. Dev. lab, Bagsvaerd	734311		kg
10 µg E ₂	811870	Apr.88	Pharm. Dev. lab, Bagsvaerd	734311		kg

Reviewer Comments:

1. The clinically tested formulation as well as the PK study formulations are the same formulation as the "to be marketed" formulation in US except for one of the inactive ingredient, Hypromellose (Hypromellose, is the control release component according to the chemistry reviewer Dr. Mitra). The "to be marketed" formulation will contain _____ whereas the clinical and PK formulations contained _____ Hypromellose. The two Types differ qualitatively.
2. The qualitative difference was discussed with Dr. Amit Mitra and he believes that both Types _____ would meet the USP specifications. The classification is internal to Novo. By the use of an internal (Novo) multivariate approach the sponsor claims that they can distinguish the Types of HPMC. _____ The variables affecting the dissolution rate are degree of substitution, salt content, iron content, moisture content, sulfated ash, viscosity, and pH of HPMC, even though all the test attributes are within the

compendial specifications (iron is not measured in the USP). Right now, the sponsor can distinguish between Type and Type (another classified Type HPMC) but not between Type and Type. They think that they would be able to distinguish between Type and Type by using a compilation of characteristics of the test attributes.

6 In Vitro Drug Release

(Volume 13 p. 143-168 p. 233-237, and summary of other pages)

Three methods have been used by the Sponsor throughout the development of Vagifem™ tablet. Method has been used for the release of clinical batches. Methods that were used for production batches later. The details of each method is tabulated in Table 3, page 9.

Two dissolution method revisions have occurred during the process of Vagifem™ development. The first revision resulted in method. This method has been used to release marketed product in Europe. The method intended to be used for the U.S. product and is now used for the release of product sold in other countries is

The reason for the first revision from method was to decrease the number from 10 tablet dissolution to 1 tablet dissolution, in order to gain better measurement of the quality of tablets. In addition paddle rotational speed was changed from 50 to 100 rpm to decrease the coefficient of variation values of the dissolution performed on 1 tablet of Vagifem™.

The result of comparison of the two methods shows no significant difference between the two methods and the same dissolution profiles are observed between the two methods (see attached graph).

The reason for the second dissolution method revision from is a change in the property of HPMC. The main inactive ingredient in Vagifem tablets is Hypromellose or Hydroxypropyl Methylcellulose (HPMC), which forms a hydrophilic matrix system (the supplier of HPMC is). Due to the natural origin of HPMC, inter-batch variations are seen within HPMC batches resulting in minor variations in the dissolution profile of the finished product. These differences are reflected as small variations in the dissolution profile but it has not been possible to identify them on certificate of analysis. Therefore, a special screening test-production of tablets in laboratory scale was performed.

Until January 1997, only batches of Type have been used for production. At present, it is not possible for the Sponsor to be supplied with HPMC, resulting in tablets complying with previously approved finished product specification for Vagifem with respect to dissolution limits. All available batches of HPMC are of Type and these are now used for production of Vagifem™. Comparing the dissolution profiles of Type resulting in a minor change in the dissolution profile. Yet, all the clinical and PK studies are performed using Type formulation.

Figures 1 and 2 show the in vitro release profile of Vagifem™ at pH 4.75 ± 0.5 for batch 4159-11 (Type HPMC) and batch GA5V427 (Type HPMC). Note, GA5V427 and 4159-

11 batches are not made at the same time. Batch 4159-11 (Type 1) was produced in 1994 and the original dissolution method was applied. For this batch to use method (a method developed July 1996) the batch had to be at least 2 years old at the time of dissolution test (see Table 3). Batch GA5V427 (Type 2) however, was produced in 1997 and the proposed dissolution method was used for this batch. At the time of dissolution test both the method and the batch were less than a year old.

The comparison of the two batches shows slower dissolution for Type 1. Therefore, the sponsor has changed the dissolution sampling time points and specification for Type 1 (from 2, 4, and 6 hours to 3, 5, and 10 hours). The methods are only different in their sampling times and the specifications. The method intended to be used for the release of the U.S. marketed product is the proposed method.

Since the two batches in Figure 1 and 2 differed in their age, to assure similarity between Type 1 and Type 2 dissolution profiles the sponsor has performed a dissolution study using method F30058E for Vagifem™ batches produced of both Type 1 (8 batches) and Type 2 HPMC (9 batches) in the Building 5A (the same time points and specifications were used). All the batches used for this study were produced during the first half of 1997.

Figure 3 shows the dissolution profile curves for the tablet batches produced of the two Types of HPMC. The pH of the medium for this method is 4.75 ± 0.05 .

Table 3. Comparison of proposed dissolution and specification method (Type 1) with the original dissolution and specification method (Type 2)

Apparatus Type → Oct. 92 July 96 Aug 97	USP Apparatus 2 USP Apparatus 2 USP Apparatus 2
Medium	: Phosphate buffer pH = 4.75 ± 0.05 Phosphate buffer pH = 4.75 ± 0.05 Phosphate buffer pH = 4.75 ± 0.05
Volume	: 500 ml ± 5 ml 500 ml ± 5 ml 500 ml ± 5 ml
Speed of Rotation	50 ± 1 rpm ($37.0 \pm 0.5^\circ\text{C}$)(10 tablets) 00 ± 2 rpm ($37.0 \pm 0.5^\circ\text{C}$)(1 tablet) 00 ± 2 rpm ($37.0 \pm 0.5^\circ\text{C}$)(1 tablet)
Sampling Time	: 2, 4, and 6 hours 2, 4, and 6 hours 3, 5, and 10 hours
Original Dissolution Specifications method:	% estradiol release after 2 hrs % estradiol release after 4 hrs % estradiol release after 6 hrs % estradiol release after 2 hrs % estradiol release after 4 hrs

Proposed Dissolution Specifications
method:

% estradiol release after 6 hrs

% estradiol release after 3 hrs¹

% estradiol release after 5 hrs¹

% estradiol release after 10 hrs¹

¹Applying the USP <724> acceptance table 1

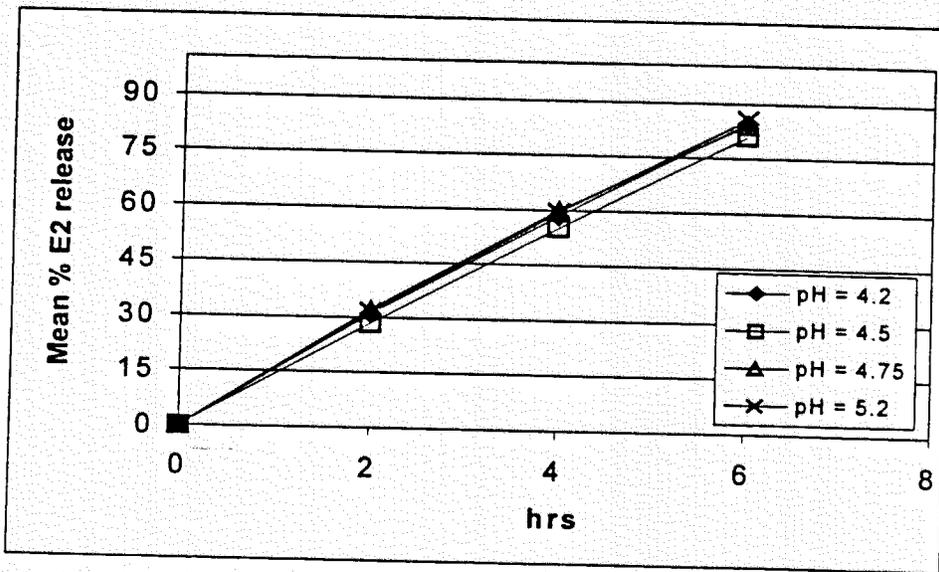


Figure 1. In vitro release profile of tablets with HPMC Type formulation. Method batch 4159-11 (produced 1994).

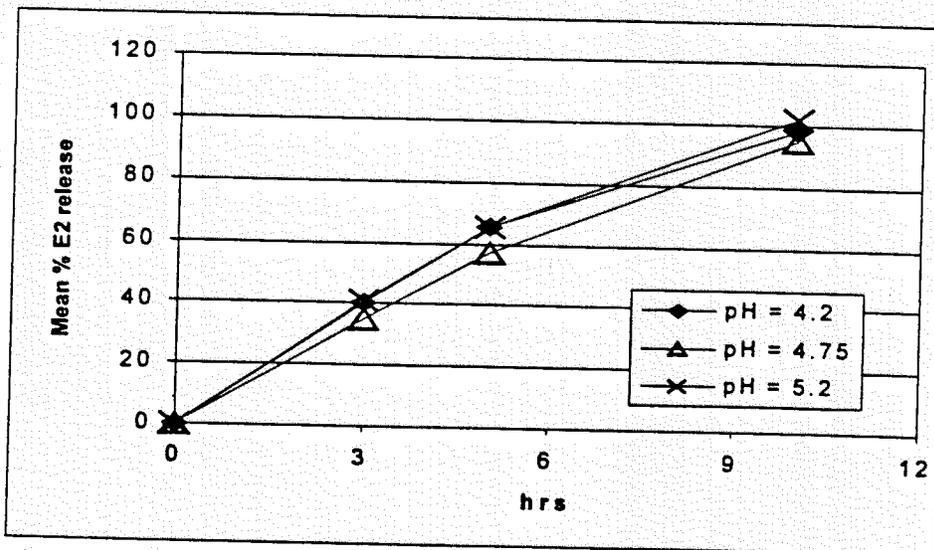
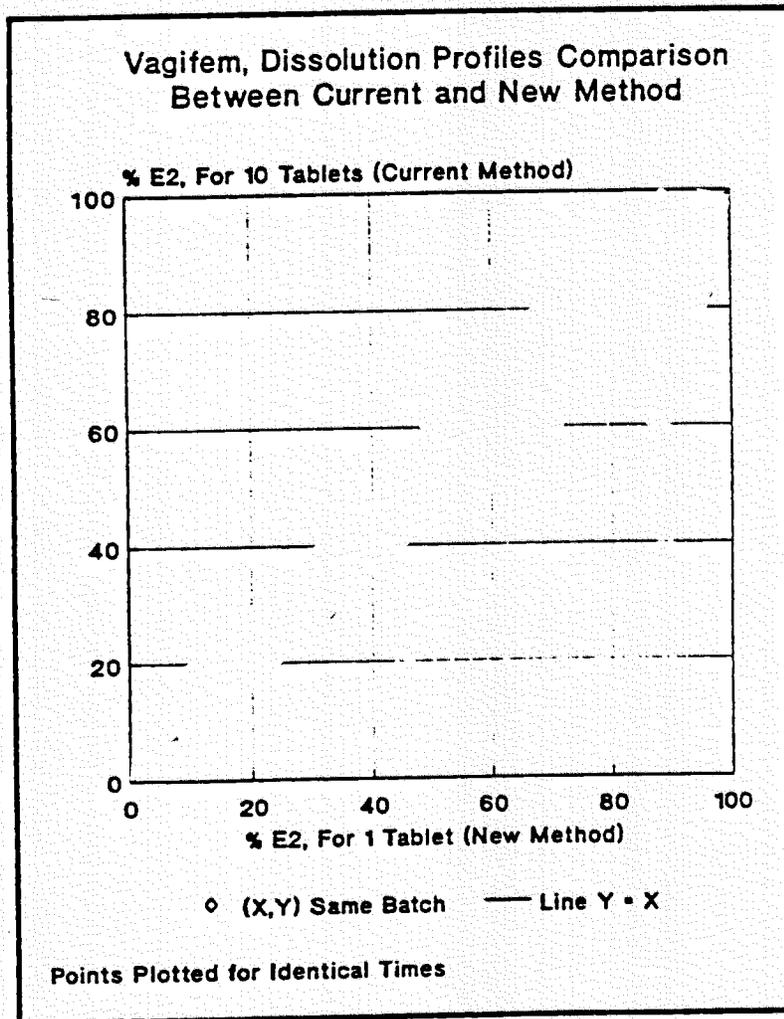


Figure 2. In vitro release profile of tablets with HPMC Type formulation. Method batch GA5V427 (stability studies were done with this batch, produced 1997).

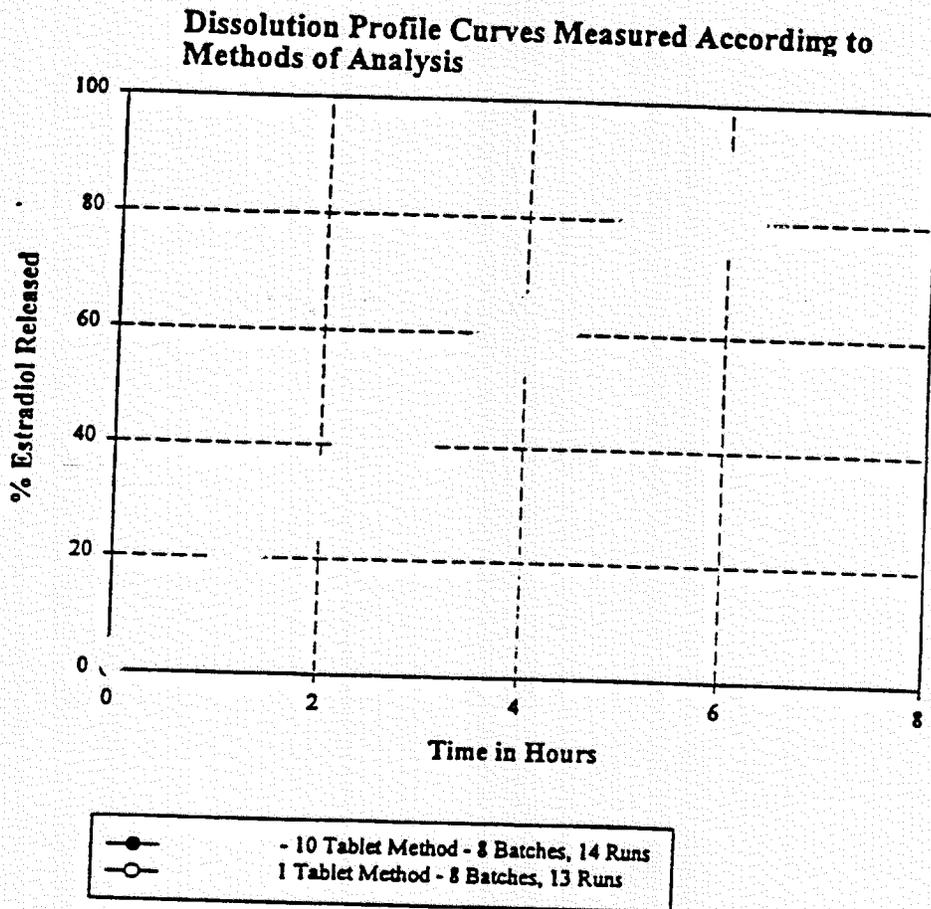
Figure 2.3



attachment.

Volume 13 - P. 160

Figure 3.1



attachment.

Volume 13 - P. 176

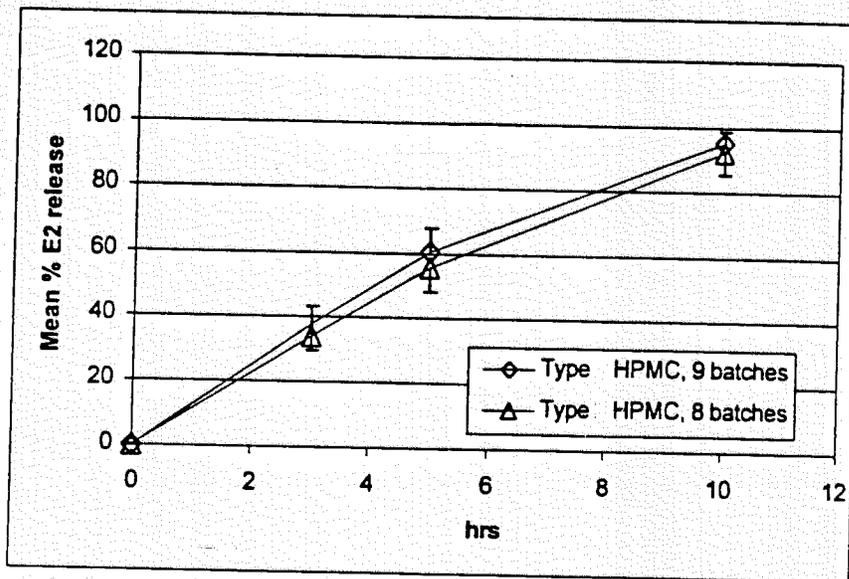


Figure 3. *In vitro* release profile of tablets with HPMC Type [redacted] formulation, using the same dissolution method [redacted]. The data points represent means and the bars represent standard of deviation of the pooled data all batches were produced in the first half of 1997.

The result of this study showed that when the sampling time points are 3, 5, and 10 hours Type [redacted] have comparable dissolution profile. The dissolution profiles comparing Type [redacted] is within acceptance criteria for similarity factor according to SUPAC, with respect to proposed method [redacted] (similarity factor = 73).

Reviewer Comments:

1. According to the published guidance¹ for modified release solid oral dosage form, the change in Hypromellose type could be considered a Level 2 change in a release controlling excipient. (Since there is no guidance for the intravaginal dosage form, the available guidance was used to set the specifications with respect to changes made in the formulation). For oral dosage form, with narrow therapeutic range (NTR) drugs, as long as an *in vitro/in vivo* correlation is established, a bioequivalence study can be waived. However, it is not clear if estradiol is a NTR drug and the route of administration is not oral but vaginal therefore,
2. To assure similar *in vivo* dissolution profile between the clinical batch (Type [redacted] and "to be marketed" batch (Type [redacted], in a fax dated 1/13/1999 the sponsor was asked to consider the following:
 - Compare the *in vitro* dissolution profiles varying the pH of the medium using the same dissolution method for both HPMC Types tablets. Where the two tested formulations are the clinical batch (Type [redacted]) and the to be marketed batch (Type [redacted])

¹Guidance SUPAC-MR: Modified Release Solid Oral Dosage Forms. Scale-Up and Post approval Changes: Chemistry, manufacturing, and Controls; *In Vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentation", page 10

- Subsequently the sponsor provided additional dissolution data to the FDA and the report was received on Feb 25, 1999. The following section highlights the result of the new dissolution data.

New in Vitro Dissolution Data:

In order to assure the physiological vaginal pH range is included in the recommended dissolution study Dr. Bennet, the medical officer was consulted. For this study pH was recommended to range from 3 to 6.8.

According to the proposed testing program of 15 January 1999 the dissolution profile of one batch of Vagifem™ produced with Type HPMC (GA5V418) and one batch produced with Type HPMC (GA5V427) were tested. The batches were tested according to Method of Analysis (testing points 3,5,10 hours).

Based on the data, the sponsor concludes there are:

1. No difference between the two profiles for Vagifem™ tablets produced with Type HPMC respectively when tested at pH 3.0, 4.75, 6.0, and 6.8. The respective f_2 test values were 82, 85, 73 and 74.
2. Complete release is seen after approximately 15 hours at pH 6.8 whereas complete release is seen after approximately 10 hours for the other pH values tested.

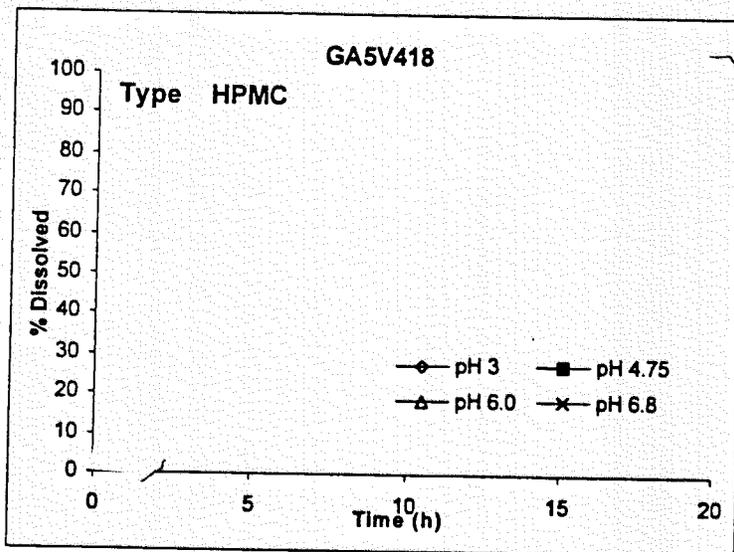


Figure 4. In vitro release profile of tablets with HPMC Type formulation, using dissolution method at multiple pH media.

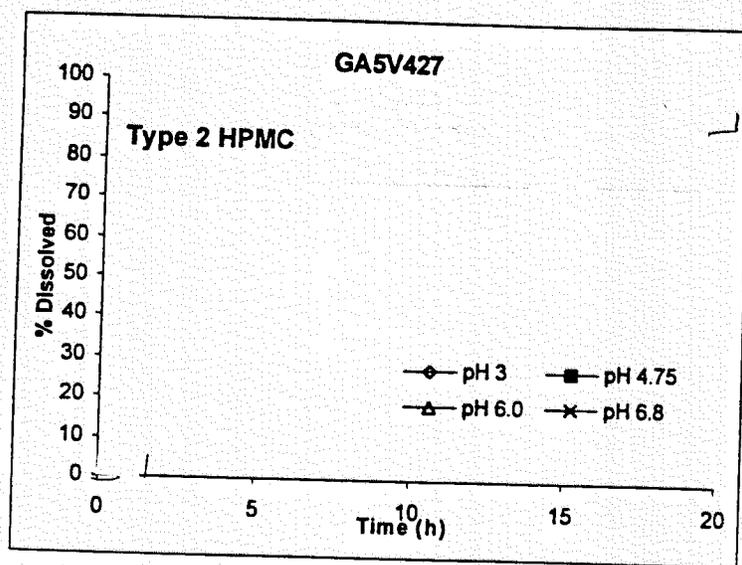


Figure 5. In vitro release profile of tablets with HPMC Type 2 formulation, using dissolution method at multiple pH media.

Reviewer Comments:

This reviewer concurs with the sponsor's conclusion and does not see the utility of additional bioequivalence studies for the following reasons:

- The similarity in *in vitro* dissolution profiles in multiple pH media covering the physiological pH range is an assurance that the formulation changes should not translate to therapeutic inequivalence.
- The low systemic concentrations and large variability of both estradiol and estrone (both about or less than observed average concentration in postmenopausal women), indicating minimal absorption and therefore minimal systemic exposure (see Pharmacokinetics section).
- Since the drug is indicated for local effect rather than systemic effect, a bioequivalence study is not likely to be able to discriminate between the two tablets of Type 2 HPMC in terms of their availability to the site of action, vagina (not blood).

However, the specifications set by the sponsor are set too wide for the proposed method. This issue was discussed with Dr. Amit Mitra the Chemistry reviewer and the conclusion of our last discussion was to recommend the sponsor to use the following dissolution specifications:

<u>Sampling Time</u>	<u>Recommended Specification</u>	<u>Sponsor Specification</u>
Hrs	%	%
Hrs	%	%
Hrs	%	%

This recommendation is based on two data sources:

- 1) The dissolution data submitted from batch GA5V418 (Type and GA5V427 (Type at pH = 4.75 (faxed March 4, 1999).
- 2) The 12 months stability data provided by the Chemistry reviewer Dr. Amit Mitra. The limitations set by the following guidance was also considered.
- 3) According to the guidance for the extended release oral dosage forms² page 17: In the absence of an IVIVC study:

"In Certain cases, reasonable deviation from the $\pm 10\%$ range can be accepted provided that the range at any time point does not exceed 25%. Specifications greater than 25% may be acceptable based on evidence that lots (side batches) with mean dissolution profiles that are allowed by the upper and lower limit of the specifications are bioequivalent".

Note: The in vitro dissolution data from the clinical batch were not helpful to set a recommended specifications since the method used is different than the one is going to be used for production in the U.S.

Dr. Amit Mitra (Chemistry Reviewer) conveyed the FDA recommended specifications to the sponsor. In response, on March 18th, 1999, the sponsor provided FDA with dissolution data from 38 production batches to justify the original proposed specifications. Based on these data and considering the variability associated with the dissolution measurements mostly at 5 hours time point, the recommended specification by FDA was revised and is as follows:

<u>Sampling Time</u>	<u>FDA Recommended Specification</u>	<u>Sponsor Specification</u>
Hrs	%	%
Hrs	%	%
Hrs	%	%

The dissolution method is:

Apparatus Type: USP Apparatus 2

Medium: Phosphate Buffer pH = 4.75 \pm 0.05

Volume: 500 ml \pm 5 ml

Speed of Rotation: 37.0 \pm 0.5°C)(1 tablet)

Sampling Times: hours

Note: It was noted by the reviewer that the sponsor may need to apply the USP Acceptance Table 1, i.e., L1, L2, or L3. USP 23 NF 18, p. 1796

² Guidance to Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. Page 17. Setting Dissolution Specification without an IVIVC.

7 Analytical Methodology

Reviewer Comments:

1. The validation of E₂, E₁ and E₁S are all performed in the same site at [redacted] Therefore cross-validation was not necessary. Prior to [redacted] quantitation, the plasma samples were extracted and ran through [redacted] This method insures more specificity and accuracy than just crude [redacted] method of quantitation.

8 Clinical Pharmacology and Biopharmaceutics

8.1 Pharmacokinetics

Prior to the two pivotal PK studies (4/S, 10/USA), the sponsor conducted three pilot studies in postmenopausal women (average 58 years old). The number of subjects were fewer than 10 for each study. The result of each study is summarized in the following paragraphs.

Study 609/ABS:

Two strengths of Vagifem™ (Vagitoris®) were compared for two weeks, once dosing per day intravaginally. The 50 µg dose in four women resulted in elevated E₂ plasma concentrations to normal fertile range (~ 140 pg/ml). In contrast, the 25 µg dose in three women showed minimal absorption and the plasma E₂ concentrations did not exceed the average postmenopausal levels. (~ 50 pg/ml). The E₁ and E₁S followed similar pattern as E₂ in both groups of treatment.

Study 021/ABS:

Urinary excretion of estrogens (E₂, E₁ and E₁S) were measured after 25 µg of Vagifem™ administration for two weeks. No consistent trend in differences in total urinary estrogen excretion was observed. Of the four subjects, two had an increase of 15 µg/day and two had a decrease of 7 µg/day. The plasma concentrations of estrogens showed minimal absorption. This study had no database and data listings.

Study 022/ATR:

The change in the vaginal fluid pH was measured after 25 µg of Vagifem™ for three weeks (one dose daily). The pH on average decreased from 6.4 to 4.5 in 9 women, indicating some local effect of the drug.

8.1.1 Single Dose and Multiple Dose

Two pharmacokinetic studies (4/S, 10/USA) were performed that evaluated the absorption, and metabolism of Vagifem™ in healthy postmenopausal women. In studies 4/S, and 10/USA a 10 µg E₂/tablet noncommercial formulation was included as a low

dose comparator. In both studies the measured estrogen levels are not corrected for baseline.

8.1.1.1 4/S

Study 4/S was a single center, double-blind, randomized, two-period crossover study to evaluate the pharmacokinetics and efficacy of Vagifem® (25 µg E₂ / tablet); the low dose comparator was a similar tablet containing E₂: 10 µg, a non commercial formulation. Plasma E₂ and E₁ levels were determined before and at 1, 2, 4, 6, 8, 10, 12, and 24 hours after the 1st and 14th doses. FSH and LH levels were determined before and after each treatment. A total of 24 healthy women with atrophic vaginitis were enrolled in and completed the study, age (≤ 75 years).

The E₂ plasma concentration-time curves following a single dose and 14 consecutive daily doses of Vagifem™ are shown in Figure 6. Peak levels were approximately 175 pmol/L (48 pg/mL) following a single dose of Vagifem®. After 14 days of treatment, only marginal absorption of E₂ could be detected, with mean levels in the upper postmenopausal range for the Vagifem™ dose.

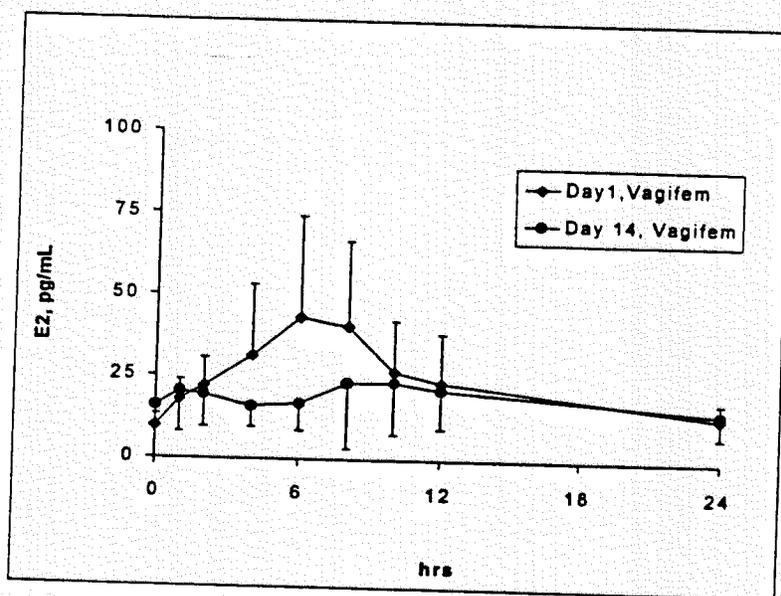


Figure 6. Mean values (n = 24) and standard of deviation of the mean E₂ concentrations following a single dose and 14th dose of Vagifem (25 µg E₂)

The E₂ and E₁ C_{max} and AUC in plasma following a single dose and 14 consecutive doses of Vagifem™ are summarized in Table 7.

Table 7. Mean AUC and C_{max} for E₂ and E₁ and Standard Deviation Concentrations Following a Single Dose and 14 doses of Vagifem™ (25 µg E₂) (4/S)

Entity measured	Single dose		14 th dose	
	C _{max} (pg/ml)	AUC (h*pg/ml)	C _{max} (pg/ml)	AUC (h*pg/ml)
E ₂	60 ± 33	583 ± 180	34 ± 18	433 ± 187

E₁	11 ± 6	164 ± 55	10 ± 5	152 ± 61
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* No peak levels were observed, the C_{max} value only refers to highest levels observed among the subjects.

Reviewer Comments:

The statistical analysis of this cross-over study showed no sequence effect, i.e., no carry-over effect. Indicating adequately long wash-out period between the two periods.

The single dose study (Day 1) indicates absorption of estradiol to the systemic circulation with a mean peak concentration (C_{max}) about, 50 pg/ml (~200 pmol/L). The mean plasma E₂ concentration after 2 weeks is stabilized (10 pg/ml). Safety evaluation indicates no side effects are associated with this plasma concentration. The estrone (E₁) concentrations do not exceed normal expected concentrations in post-menopausal women (E₁ concentrations can get as high as 100 pg/ml in post-menopausal women). Low systemic absorption of E₂ has resulted in low levels of E₁ (little formation), the primary reversible metabolite of 17β-estradiol.

Lower area under concentration-time curve (AUC) for E₂ after 14th dose suggests decrease in absorption. This can be due to saturation of absorption or due to maturation of the cells at vaginal epithelium. The sponsor believes the latter is occurring, using results of cell maturation scales from pap smears. Sponsor has used the epithelial cell maturation as a surrogate pharmacodynamic parameter to indicate the effectiveness of Vagifem. These results are evaluated by the medical officer (Dr. R. Bennet).

8.1.1.2 10/USA

This study evaluated the pharmacokinetics of estradiol following administration of Vagifem™ and 10µg estradiol over 12 weeks. One daily dose for 2 weeks followed by 10 weeks of twice-weekly maintenance therapy. For Study details, see Attachment. The results are summarized in Table 8 and Table 9.

Table 8. Mean (±S.D.) pharmacokinetic parameters (0-24 hours) for serum estradiol (E₂) concentrations (uncorrected for baseline) at week 0, 2, and 12, following administration of Vagifem™ 25µg and 10µg estradiol.

Time point	Parameter	Vagifem™ 25 µg E₂	10µg E₂
Week 0 (day 1) (single dose)	AUC ₀₋₂₄ (pg.hr/mL)	538(265)	349(107)
	C _{max} (pg/mL)	51(34)	35(17)
	T _{max} (hr)	15(9)	9(5)
Week 2	AUC ₀₋₂₄ (pg.hr/mL)	567(246)	255(102)
	C _{max} (pg/mL)	47(21)	18(7)
	T _{max} (hr)	8(8)	7(8)
Week 12	AUC ₀₋₂₄ (pg.hr/mL)	563(341)	264(120)
	C _{max} (pg/mL)	49(27)	22(17)
	T _{max} (hr)	13(6)	10(8)

Table 9. Mean (\pm S.D.) pharmacokinetic parameters (0-24 hours) for serum estrone (E_1) concentrations (uncorrected for baseline) at week 0, 2, and 12, following administration of Vagifem™ 25 μ g and 10 μ g estradiol.

Time point	Parameter	Vagifem™ 25 μ g E_2	10 μ g E_2
Week 0 (day 1) (single dose)	AUC ₀₋₂₄ (pg.hr/mL)	649(230)	519(190)
	C _{max} (pg/mL)	35(12)	26(9.0)
	T _{max} (hr)	14(9)	9(7)
Week 2	AUC ₀₋₂₄ (pg.hr/mL)	744(267)	558(206)
	C _{max} (pg/mL)	39(13)	30(10)
	T _{max} (hr)	7(8)	6(7)
Week 12	AUC ₀₋₂₄ (pg.hr/mL)	681(271)	568(203)
	C _{max} (pg/mL)	35(12)	31(14)
	T _{max} (hr)	12(11)	9(9)

Reviewer Comments:

1. Estradiol pharmacokinetic parameters suggest that estradiol does not accumulate following repeat administration of Vagifem™.
2. Estradiol serum levels after administration of Vagifem™ do not significantly exceed post-menopausal levels.

Reviewer Conclusion of the PK Studies:

The results of the two pharmacokinetics studies (4/S, and 10/USA) are similar with respect to E_2 levels and indicate low systemic exposure of Vagifem™. This is in agreement with the sponsor's conclusion with respect to the extent of absorption.

The estrone (E_1) plasma levels were about 3-4 fold higher in 10/USA study versus 4/S study. This is more likely due to the difference in the E_1 assay sensitivity between two PK studies (validation of E_1 assay for 4/S study was not available). Alternatively the difference in E_1 plasma concentrations could also be due to differences in the extent metabolism from E_2 to E_1 between the two study subjects (subjects in 10/USA group were younger). The difference in E_1 concentration is not of concern with this product since E_1 is about 3-10 fold lower than E_2 in its pharmacological activities. In addition, E_2 systemic concentrations are similar in both PK studies and both E_1 and E_2 levels in study 10/USA are within normal concentration range in postmenopausal women.

8.2 Protein Binding

This information was extracted from literature by the sponsor. No protein binding studies were submitted in this NDA.

Summary of literature:

Estrogens are specifically bound with high affinity to sex-hormone binding globulin (SHBG) or loosely (non-specifically) bound to serum albumin. According to the literature, 37% of E_2 is bound to SHBG, 61% to albumin and only 1-2 % is free to diffuse

across cell membranes. E₁S has the highest affinity for albumin with more than 90% of circulating levels bound to albumin.

8.3 Bioavailability and Bioequivalence

8.3.1 Absolute/Relative Bioavailability

Absolute and / or relative bioavailability studies were not performed

8.3.2 Bioequivalence

The formulation change is minor and involves only one of the inactive components, qualitatively. There is no guidance for this Type of change concerning intravaginal administration route. However, based on the Guidance to the industry, for oral dosage form of drugs, these Type of minor changes do not require bioequivalence studies, as long as dissolution profiles are comparable between the two formulations. The issue was communicated to the sponsor and in vitro dissolution studies were carried at different pH of the medium using the same sampling time and dissolution method, in order to assure similar rate of release between the two tablet formulations, containing Type _____ HPMC. This issue is already addressed in the "In Vitro Dissolution" section of this review.

8.3.3 Food Effect

No food effect studies were performed (not applicable).

8.3.4 Dose-Proportionality

Only one dose is going to be marketed for Vagifem™ (25 µg estradiol). However, for clinical studies both 10 and 25 µg doses are used.

8.4 Special Population

Study 10/USA had slightly younger women included, average age = 52 years old ranging 45-63 years. Study 4/S included women of 75 years of age or younger.

8.5 Metabolism

No in vitro metabolism studies were performed. However, the C_{max} and AUC of two metabolites E₁S and E₁ were characterized. Sponsor relied on literature for the information on metabolism of estradiol.

Summary of literature:

The principal cytochrome P450 isoforms involved in the metabolism of E₂ are CYP3A4 and CYP1A2. Although no clinical trials have been conducted, the metabolism of estradiol by the cytochrome P450 isoforms CYP1A2 and CYP3A4 suggest that drugs like ketoconazole, itraconazole, erythromycin, and grapefruit juice are likely to inhibit the metabolism of estradiol. It should be noted that during long term treatment with

Vagifem™ there is minimal absorption of estradiol, and the potential interactions described above are therefore not likely to be of clinical relevance.

8.6 Drug Interaction

Drug interaction studies were not performed.

8.7 Population Pharmacokinetics

Not performed.

8.8 PK-PD Relationship

No analysis was performed with respect to concentration-effect relationship. The assumption is that the effect is local rather than systemic.

**APPEARS THIS WAY
ON ORIGINAL**

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pages of trade

secret and/or

confidential

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information

Attachments

Attachment A.

Synopses of individual studies

- I. **Study Name:** 4/S: a Single dose study for 14 days to determine PK and efficacy.
- II. **Volumes:** 19

TITLE OF TRIAL: Local Treatment of Atrophic Vaginitis With Two Low-Dose Oestradiol Vagitories. Vagifem. A pharmacokinetic and pharmacodynamic study. VAG/PD/4/S (SVAG/006/ABS)

TRIAL CENTER:

TRIAL PERIOD: 1988-89

CLINICAL PHASE: II

OBJECTIVES: The primary objective was to evaluate the pharmacokinetics of Vagifem 10 µg and 25 µg in women with symptoms of estrogen deficiency-derived atrophic vaginitis. The secondary objective was to evaluate the effect of gonadotrophins and cytology from vaginal and urethral mucosal smears. The effect of Vagifem on symptoms related to estrogen deficiency-derived atrophic vaginitis was also evaluated.

METHODOLOGY: This was a single-center, double-blind, controlled, cross-over study. Women were randomized to daily treatment with either Vagifem 10 µg or 25 µg tablets for 2 weeks followed by a minimum period of 12 weeks wash-out after which 2 weeks of daily treatment was repeated with the alternative preparation. At each visit, blood samples for determination of E₁ and E₂ were taken before the application of the first tablet at baseline and after 1, 2, 4, 6, 8, 10, 12, and 24 hours to assess the extent of absorption of estradiol from the tablets.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED): 24 women were planned and analyzed. No women dropped out during the study. The subjects were 75 years old or younger.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Postmenopausal women not more than 75 years old with estrogen deficiency-derived atrophic vaginitis and not requiring systemic hormone replacement therapy.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: 10 µg (estradiol) and 25 µg Vagifem™ (estradiol) intravaginally daily for 2 weeks, cross-over.

DURATION OF TREATMENT: 16 weeks (two 2-weeks treatment periods separated by a 12-weeks wash-out period).

CRITERIA FOR EVALUATION - 1) PHARMACOKINETICS: Determination of FSH/LH, estrone (E₁), and estradiol (E₂) levels. **2) EFFICACY -** Assessment of symptoms of atrophic vaginitis, vaginal and urethral smears.

CRITERIA FOR EVALUATION - SAFETY: The occurrence of adverse effects.

STATISTICAL METHODS:

Statistical comparisons of pharmacokinetic data were made using the statistical software package SAS®. Analysis of variance usually was performed with the general linear model procedure to assess treatment effects. In crossover studies, sequence, period, and treatment effects were included in the statistical models. Effects were declared statistically significant if the associated p-value was ≤ 0.05.

Statistical analysis of the hormone kinetic data was done on the logarithm of the measurements to stabilize variance over time. An ANOVA of the cross-over design was performed at each hourly

evaluation for weeks 0 and 14 in one analysis and for weeks 2 and 16 in another analysis. The cross-over design was analyzed for sequence effect, difference between the two periods, and difference between treatments. A one-way ANOVA was done to determine if there were significant changes between measurements at different time points. A t-test was used to determine significant differences in AUC before and after treatment. Changes in FSH and LH were analyzed by t-test, vaginal symptoms by chi-square test, and changes in vaginal cytology by paired t-test

PHARMACOKINETIC CALCULATION:

The area under the concentration-time curve over the 24-hour period after dosing (AUC) was calculated using linear trapezoidal rule. For subjects with incomplete data, the AUC was calculated from the first time point with data to the last time point with data. The maximum concentration, C_{max} , and the time to maximum concentration, t_{max} , were read directly from the observed concentration-time curve for each subject. In the computation of AUC and C_{max} for E_2 and E_1 , no adjustments to the data were made for pre-treatment levels of these endogenous hormones.

ANALYTICAL METHOD OF QUANTITATION:

(Volume 13). Details of the method is described in the "Analytical Methodology" section of this review.

PHARMACOKINETIC RESULTS:

- The ANOVA test of the cross-over design resulted in no detectable sequence effect, i.e. the 3 months wash-out period has been long enough to ensure that there is no carry-over effect between the two periods. Therefore the data from weeks 0 and 14 (single dose results) and weeks 2 and 16 (MD, 14th day results) were pooled to evaluate PK of single dose and multiple dose at both 10 and 25 µg estradiol doses in 24 subjects.
- After first dose of Vagifem 25 µg, initially some absorption of estradiol is seen with a peak level C_{max} of about 60 pg/mL (~220 pmol/L) estradiol, no peak was detectable after 2 weeks of treatment and the mean E_2 level was stabilized in the upper postmenopausal range (Figure 1 & Table 1).
- A peak estradiol (C_{max}) for Vagifem 10 µg was about 26 pg/ml (108 pmol/L) after first dose, after 2 weeks of treatment (Figure 2 & table 2) the concentrations reach steady-state.
- For both treatment groups, area under concentration-time (AUC) curve value was significantly lower after 14th dose compared to the first dose. The sponsor concludes that systemic absorption and therefore systemic exposure is minimal. They also conclude that decrease in the absorption is because of increase in the estrogenization of vaginal mucosa.
- The T_{max} is achieved after approximately 10 ± 6 hours in both 10 and 25 µg groups.
- For estrone (E_1) all values for both treatment groups were below or slightly above the limit of quantitation, both for after single and multiple dose (14th dose). Similarly, AUC values for both treatment groups as well as after SD and MD showed no significant change.
- FSH and LH were significantly lowered in the 25 µg group, whereas only FSH was lowered in the 10 µg group. In all cases, FSH and LH were within normal postmenopausal range.

EFFICACY RESULTS:

- Vaginal cytology was almost normalized following Vagifem treatment; however, the effect on urethral cytology was less pronounced. Significant improvement was seen in vaginal atrophy, dryness, and soreness in both treatment groups. A significant decrease in dyspareunia occurred in both treatment groups. Responses for vaginal irritation and discharge were less clear. There were no significant differences between the two treatments in the effects on symptoms.

SPONSOR'S CONCLUSIONS: The absorption of estrogen from Vagifem containing 10 µg or 25 µg E₂ was very low following normalization of the vaginal mucosa.

Review:

The sponsor believes that the decreased absorption as reflected by lower plasma levels of vagifem (E₂) after two weeks administrations compare to the single dose on the first day, is due to estrogenization of vaginal mucosa, i. e., normalization of vaginal cytology and improvement in the symptoms associated with vaginal atrophy. This reviewer refers the evaluation of estrogenization of vaginal mucosa to the medical officer. If medical officer finds that the cytology results reflect normalization of vagina, this reviewer concurs with the sponsor's conclusion. Conversely, if vagifem is actively absorbed in the vaginal cavity, saturation of the absorption may also result in plasma concentration of vagifem that is lower after two weeks of administration (another possible mechanism for the decreased absorption)

In postmenopausal women the estrone plasma concentration could be as high as 100 pg/ml and the mean estradiol is about 50 pg/ml (200 pmol/L). Administration of Vagifem™ and 10 µg estradiol resulted in peak plasma concentrations about or lower than expected in the untreated postmenopausal population, indicating no accumulation of the drug systemically followed by little formation of estrone in the study subjects (4/S).

Table 1. Mean AUC and C_{max} for E₂ and E₁ and Standard Deviation Concentrations Following a Single Dose and 14 doses of Vagifem™ (25 µg E₂) (4/S)

Entity measured	Single dose		14 th dose	
	C _{max} (pg/ml)	AUC (h*pg/ml)	C _{max} (pg/ml)	AUC (h*pg/ml)
E ₂	60 ± 33	583 ± 180	34 ± 18	433 ± 187
E ₁	11 ± 6	164 ± 55	10 ± 5	152 ± 61

* No peak levels were observed, the C_{max} value only refers to highest levels observed among the subjects.

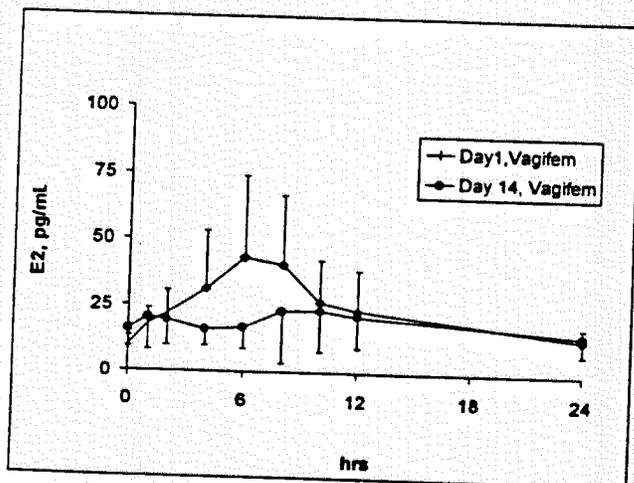


Figure 1. Mean values (n = 24) and standard of deviation of the mean E₂ concentrations following a single dose and 14th dose of Vagifem (25 µg E₂)

Table 2. Mean AUC and C_{max} for E_2 and E_1 and Standard Deviation Concentrations Following a Single Dose and 14 doses of $10 \mu\text{g } E_2$ (4/S)

Entity measured	Single dose		14 th dose	
	C_{max} (pg/ml)	AUC (h*pg/ml)	C_{max} (pg/ml)	AUC (h*pg/ml)
E_2	26 ± 10	371 ± 110	20 ± 6	312 ± 83
E_1	8 ± 4	140 ± 41	9 ± 4	141 ± 32

* No peak levels were observed, the C_{max} value only refers to highest levels observed among the subjects.

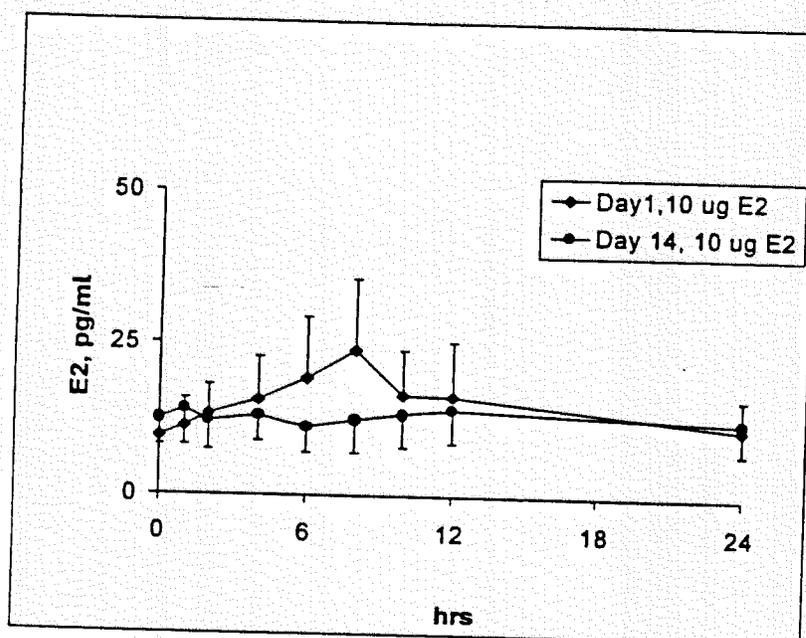


Figure 2. Mean values (n = 24) and standard of deviation of the mean E_2 concentrations following a single dose and 14th dose of $10 \mu\text{g } E_2$.

Attachment B.

Study No.: VAG/PD/10/USA

Study Title:

A Randomized, Double-Blind, Parallel-Group Study Comparing the Absorption of 17- β Estradiol During Treatment With E2: 10 μ g and Vagifem™ 25 μ g

Study Synopsis

See attachment.

Results:

Table I. Mean (\pm S.D.) pharmacokinetic parameters (0-24 hours) for serum estradiol (E₂) concentrations (uncorrected for baseline) at week 0, 2, and 12, following administration of Vagifem™ 25 μ g and 10 μ g estradiol.

Time point	Parameter	Vagifem™ (25 μ g)	10 μ g estradiol
Week 0 (day 1) (single dose)	AUC ₀₋₂₄ (pg.hr/mL)	538(265)	349(107)
	C _{max} (pg/mL)	51(34)	35(17)
	T _{max} (hr)	15(9)	9(5)
Week 2	AUC ₀₋₂₄ (pg.hr/mL)	567(246)	255(102)
	C _{max} (pg/mL)	47(21)	18(7)
	T _{max} (hr)	8(8)	7(8)
Week 12	AUC ₀₋₂₄ (pg.hr/mL)	563(341)	264(120)
	C _{max} (pg/mL)	49(27)	22(17)
	T _{max} (hr)	13(6)	10(8)

Table II. Table I. Mean (\pm S.D.) pharmacokinetic parameters (0-24 hours) for serum estrone (E₁) concentrations (uncorrected for baseline) at week 0, 2, and 12, following administration of Vagifem™ 25 μ g and 10 μ g estradiol.

Time point	Parameter	Vagifem™ (25 μ g)	10 μ g estradiol
Week 0 (day 1) (single dose)	AUC ₀₋₂₄ (pg.hr/mL)	649(230)	519(190)
	C _{max} (pg/mL)	35(12)	26(9.0)
	T _{max} (hr)	14(9)	9(7)
Week 2	AUC ₀₋₂₄ (pg.hr/mL)	744(267)	558(206)
	C _{max} (pg/mL)	39(13)	30(10)
	T _{max} (hr)	7(8)	6(7)
Week 12	AUC ₀₋₂₄ (pg.hr/mL)	681(271)	568(203)
	C _{max} (pg/mL)	35(12)	31(14)
	T _{max} (hr)	12(11)	9(9)

Reviewer Comments:

3. Estradiol pharmacokinetic parameters suggest that estradiol does not accumulate following repeat administration of Vagifem™.
4. Estradiol serum levels after administration of Vagifem™ do not significantly exceed post-menopausal levels

**APPEARS THIS WAY
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Group Leader Memorandum

NDA: 20-908

Drug: Vagifem™
Estradiol Vaginal Tablets

Indication: Treatment of atrophic vaginitis due to post-menopausal estrogen deficiency

Dose: 25 ug tablet

Device: A vaginal insertor is used to deliver the tablet intravaginally

Regimen: One tablet intravaginally daily for the first 14 days followed by one tablet intravaginally twice weekly thereafter

Applicant: Novo Nordisk Pharmaceuticals Inc.

Original Submission: 5/28/98

Review Completed: 3/19/99

MAR 26 1999

Background

Vagifem™ is a low-dose estradiol vaginal tablet designed to treat atrophic vaginitis associated with estrogen deficiency in menopausal women. The product is marketed in 35 countries and approximately million doses have been distributed over eight years. It is recognized that some post-menopausal women do not have hot flashes or do not wish to take systemic estrogen replacement therapy due to side effects. These women may suffer, however, from vaginal dryness and irritation and thus may desire a local therapy that minimizes their systemic exposure to estrogen. Vagifem was developed for such women.

Similar products include Estring®, a vaginal ring which contains a reservoir of 2 mg estradiol, designed to be released over 3 months. Pivotal studies for Estring® compared to a synthetic conjugated estrogen cream and demonstrated comparable improvement in local vaginal symptoms. Ogen® vaginal cream is approved for the treatment of vulval and vaginal atrophy, as is Ortho® dienestrol cream and Premarin® vaginal cream. Each of these products are designed to be used initially daily, the 2-3 times per week for control of symptoms. Importantly, each of these product package inserts instructs the user to attempt to discontinue or taper medication at 3- to 6- monthly intervals.

A dose regimen /component comparison of these products follows:

Vagifem™ contains 25 ug estradiol taken daily for 2 weeks followed by 25 ug twice weekly thereafter
Estring® designed to release 7.5 ug estradiol in a stable manner over 24 hours

Ogen® vaginal cream contains 3-6 grams of estropipate, instructions for use do not specify the dosing regimen

Ortho Dienestrol® cream contains dienestrol (a synthetic estrogen) 0.01% applied daily initially, then designed for use several times per week

Premarin® vaginal cream: 0.625-1.25 mg conjugated estrogens applied daily for 3 weeks with 1 week off

Notably, only Vagifem contains data from a placebo-controlled trial to support its efficacy. The other products either compared to active controls, or are DESI approved products with no controlled clinical trial data to support their efficacy.

Review of Clinical Studies Regarding Efficacy

The sponsor performed a total of 19 clinical trials, of which 8 were adequate and well-controlled. Of the 8 controlled clinical trials, two were pharmacokinetic trials while six were designed to show safety and efficacy. These six trials involved a total of 386 women who received treatment with Vagifem. Two of these six trials were considered pivotal, and are the subject of this secondary review.

STUDY 9/USA

Study 9/USA compared two doses of Vagifem (10 ug and 25 ug) to placebo. The trial enrolled 230 subjects. The primary efficacy endpoint was the relief of vaginal symptoms based on a composite score of dryness, soreness, and irritation measured at week 7. Each symptoms was ranked on a scale: 0=none, 1=mild, 2=moderate, and 3=severe. Efficacy results are summarized below:

	Placebo (n=47)	Estradiol 10 ug (n=92)	Estradiol 25 ug (Vagifem™) (n=91)
Baseline Composite Symptom Score	1.93	1.82	1.85
Week 7 Composite Symptom Score	1.08	0.79	0.63
Change: Baseline to week 7*	-.85	-1.03	-1.22
Week 12 Composite Symptom Score	1.06	0.56	0.46
Change: Baseline to Week 12	-.87	-1.26	-1.39

*primary endpoint

The placebo effect observed was remarkable. Nonetheless, Vagifem resulted in an additional improvement in vaginal symptoms of 0.37 units over placebo. This result was statistically significant ($p=0.016$). The clinical relevance of such a modest change, however, was questioned during the review process.

The strength of the application was supported by the fact that each of the four individual vaginal symptoms of dryness, dyspareunia, irritation, and soreness consistently showed a greater improvement by week 7 in the Vagifem arm vs placebo. Dose-responsiveness was also supportive, with the 10 ug estradiol arm showing results which were intermediate between placebo and the higher 25 ug dose arm. The lowest effective dose of Vagifem does indeed appear to be very close to 25 ug since the 10 ug dose failed to show efficacy over placebo. Such a close approximation of the lowest effective dose is a favorable aspect of this application.

Results at week 12 demonstrated that the improvement in the Vagifem arm over placebo was slightly more marked than that noted at week 7, also supportive of efficacy and the sustained nature of these findings. Secondary efficacy analyses showed that the percentage of patients with mild or no symptoms by the end of the 12 week trial was consistently greater in the Vagifem arm than in placebo for each of the three major symptoms (dryness: 87% vs 60%, soreness 94% vs 74%, and irritation 96% vs 76%). Finally, the biological endpoint of vaginal cytology also demonstrated the effects of Vagifem over placebo for promoting maturation of vaginal cells. In light of these multiple supportive analyses, this reviewer believes that the modest effect of Vagifem over placebo is nonetheless relevant and meaningful.

STUDY 5/CAN

The second, supportive clinical trial, Study 5/CAN compared Vagifem to Premarin vaginal cream (referred to in this review as "Premarin VC"). Patients in the Vagifem group inserted one tablet intravaginally daily

for 2 weeks, then one tablet twice weekly for the following 22 weeks. Subjects in the Premarin VC group inserted 2 grams of cream (the maximum recommended dose) daily for 3 weeks, then withheld application for one week, and continued this cyclical regimen for the duration of the 24 week trial. The primary endpoint was again the relief of vaginal symptoms based on the change in composite score for the three symptoms of dryness, soreness, and irritation as measured at week 12. Results of the primary efficacy endpoint analysis are shown below:

Vaginal Symptom Score Improvement: Study 5/CAN

	Premarin Vaginal Cream (n=80)	Vagifem (n=80)
Baseline Composite Symptom Score	1.63	1.68
Week 12 Composite Symptom Score	0.63	0.52
Change: Baseline to Week 12*	-1.00	-1.16

*Primary Endpoint

The absolute difference between Premarin VC and Vagifem treatment arms regarding the improvement in vaginal symptom score from baseline at week 12 was -.16 with a 95% CI of (-.40, 0.08). The upper limit of 0.08 was well within the prespecified 95% CI of 0.3, which was accepted as defining equivalence. Although this study was designed as an equivalence trial, it was noted that many patients in the Premarin arm discontinued the study prematurely due to adverse events or "noncompliance." In fact, 90% of the Vagifem patients completed the study, while only 68% of Premarin VC patients completed the trial. This led to some concern that the claim of equivalent efficacy could be biased due to the differential drop-out rate in the Premarin cream arm. In addition, there was concern from FDA statisticians that vaginal cytology maturation indexes were more pronounced in the Premarin cream arm, suggesting that biologically the two preparations were not comparable. FDA clinicians placed more emphasis on the relief of clinical symptoms as the primary clinically relevant endpoint, and felt that the biological endpoint of vaginal cytology did not have as much clinical relevance. Finally, there was concern that the trial was not blinded, and that the comparison of a subjective endpoint would be less valid. Realistically, however, it would have been impossible to double-blind this trial, since the use of a placebo cream could have interfered with the absorption of Vagifem.

Interestingly, this study showed that the Vagifem patients had lower systemic estradiol levels than the Premarin VC patients. By the end of the 24 week study, for example 5% of Vagifem vs 47% of Premarin VC patients had serum estradiol levels which exceeded the normal postmenopausal range. This supports the conclusion that Vagifem may act via a more localized mechanism, and nonetheless be quite effective (and safe).

Review of Clinical Studies Regarding Safety

Vagifem was safe and well tolerated in the clinical studies. There were no safety concerns raised in the clinical trials regarding the device used to insert Vagifem (such as perforations, etc). I agree with the reviewing medical officer that the critical safety issue is related to the systemic exposure of estrogen with this product.

Although serum estradiol levels above the postmenopausal range were infrequent in the Vagifem treated subjects, they did sometimes occur. Thus, there can be systemic absorption of estradiol from the vagina in subjects who take Vagifem, and therefore labeling for this product needs to reflect the class-labeling safety concerns for all estrogen drug products.

In the U.S. placebo controlled study, only 32 Vagifem and 21 placebo subjects had endometrial biopsies. One of 32 Vagifem biopsies showed endometrial hyperplasia and a second Vagifem patient developed a proliferative endometrium after 12 weeks of drug exposure. No such findings were noted in the placebo arm. In the Canadian trial, only 49 Vagifem subjects and 49 Premarin VC subjects had endometrial biopsies performed. One case of proliferative endometrium was noted in the Vagifem arm, while there were 2 cases of hyperplasia and 11 cases of proliferative endometrium in the Premarin VC arm.

Although Vagifem provides a low level of systemic estrogen exposure, it has demonstrated some effect on the endometrium. Although the sponsor presents data on patients who have received Vagifem as long as 52 weeks, the biopsy follow-up of these subjects is very limited. In addition, there are two reports of malignant endometrial neoplasms and 2 reports of endometrial hyperplasia noted in post-marketing surveillance of this product in other countries. Recommendations for the use of this product should clearly reflect the need to re-evaluate the need for continued therapy every 3-6 months (as with other estrogen products for this indication).

Conclusions:

1. Vagifem is superior to placebo for the treatment of atrophic vaginitis due to postmenopausal estrogen deficiency.
2. Vagifem is no worse than Premarin vaginal cream for the treatment of symptoms of atrophic vaginitis.
3. There were more premature discontinuations in the Premarin VC arm compared to Vagifem (31% vs 10%) in the comparative study of these two agents. Although this was not a pre-specified claim, it is a meaningful finding, particularly since the majority of discontinuations in the Premarin arm were for adverse events or noncompliance. Thus, I agree with this information being described in the Vagifem label.
4. The sponsor has agreed to labeling changes which will simply compare Vagifem to an unspecified "active comparator." This is also acceptable and preferable, given the concerns raised in the review process about the unblinded nature of the study and the differential rates of loss-to-followup between arms.

I concur with the medical officer that Vagifem be approved for the treatment of atrophic vaginitis due to postmenopausal estrogen deficiency.

MS M.D.
Marianne Mann, M.D.
Deputy Director, HFD-580

Addendum:

The statistical reviewer raised several concerns that merit additional comment:

1. The treatment-by-center interaction in the U.S. placebo-controlled trial
The reviewer noted that one center (Center 8, one of the largest centers) had the most positive results for Vagifem, that irritation scores were higher at this center, and that correlations between the scores of dryness, soreness, and irritation were stronger at Center 8. This center was actually one of the sites inspected for this NDA, and no unusual or suspicious findings were noted. When the statistical reviewer excluded the patients from Center 8, a smaller treatment effect was noted which was nonetheless significant statistically. This reviewer therefore does not find the treatment-by-center interaction so concerning to require an additional placebo-controlled trial.
2. Lack of double-blinding in the Canadian active comparative trial
Although this is an important finding to keep in mind as one interprets the Canadian trial results, it is equally important to recognize that double-blinding could not have been performed in this trial. A placebo vaginal cream, for example, would have interfered with the vaginal absorption of Vagifem tablets.

3. Lack of a well-defined endpoint in the Canadian active comparative trial
The product is indicated for the relief of vaginal symptoms of dryness, soreness, and irritation—which, due to their subjective nature, are difficult to define with clarity. The statisticians therefore questioned the relevance of the more objective endpoint of vaginal cytology. It was explained that vaginal cytology may correlate better with systemic estrogen exposure, rather than with actual clinical efficacy for the relief of vaginal symptoms. Therefore, the finding that Premarin vaginal cream resulted in improved vaginal cytology versus Vagifem does not imply an enhanced clinical benefit of Premarin for the relief of vaginal symptoms. It may instead simply reflect a higher systemic exposure to estrogen in the Premarin arm.

4. Lack of an active control whose efficacy has been proven in a double-blind placebo-controlled trial
There is no other approved product for this condition which had efficacy demonstrated in a placebo-controlled trial.

These issues were discussed in detail at several meetings with clinicians and statisticians.

JS/ M.D.
Marianne Mann, M.D.
Deputy Director, HFD-580

Memo to the Record

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Date: March 26, 1999
To: HFD-580
From: Sam H. Haidar, R.Ph., Ph.D.
RE: NDA 20-908

MAR 26 1999

The *in vitro* dissolution specification for Vagifem™, as proposed by the sponsor in a fax dated March 25, 1999 are acceptable. Similarly, labeling changes as reflected by Edition 3/19/99 of the Vagifem™ labeling are acceptable; however, we recommend the addition of *Pharmacokinetics* subheading under Clinical Pharmacology prior to Absorption.

/S/

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

/S/

3/26/99

cc:
NDA 20-908
HFD-870 (M. Chen, A. Parekh, S. Madani, S. Haidar)
HFD-580 (J. Mercier, Bennett)
CDR (Barbara Murphy For Drug)

3. The proposed labeling conforms to DRUDP internal guidance regarding the formatting of the Pharmacokinetics section.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) is of the opinion that the provided information is appropriate to support the filing of NDA 20-908. The following comments, however, should be communicated to the sponsor as appropriate:

1. Dissolution profiles for the biobatches showing sampling times every 2 hours until a minimum of % of the estradiol is released from the tablets should be submitted.
2. To facilitate the review, we request that the summary of human pharmacokinetics/bioavailability section, individual study report summaries and the proposed labeling be submitted in Microsoft Word format (Version 7), on 3.5 disks. Additionally, we request the raw data of individual studies in Excel, version 5, format.

cc:

NDA 20-908

HFD-870 (M. Chen, A. Dorantes, S. Haidar)

HFD-580 (Bennett R., Markow J.)

CDR (Barbara Murphy for Drug)