

## REQUEST FOR TRADEMARK REVIEW

**To:** Labeling and Nomenclature Committee  
Attention: Dr. Daniel Boring, Chair, HFD-530, Corporate Building, Room N461

**From:** Division of Reproductive and Urologic D. P./HFD-580  
Attention: Dr. Amit K. Mitra Phone: (301) 827-4238

**Date:** 30-Sept-1998

**Subject:** Request for Assessment of a Trademark for a Proposed Drug Product

**Proposed Trademark:** Vagifem **NDA #:** 20-908

**Established name, including dosage form:** Estradiol vaginal tablet

$C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$   
F.W. = 281.4 g/mol

Estra-1,3,5(10)-triene-3,17-diol, (17 $\beta$ ), hemihydrate

**Other trademarks by the same firm for companion products:** - None

**Name and address of applicant:** Novo Nordisk Pharmaceuticals, 100 Overlook Center, Suite 200, Princeton, NJ 08540-7810

**Indications for Use (may be a summary if proposed statement is lengthy):** Moderate to severe vasomotor symptoms associated with the menopause and in the treatment of vulvar and vaginal atrophy in women with intact uterus

**Dosage Form:** Vaginal tablet /**Strengths:** 25  $\mu$ g /**Route of Administration:** Vaginal /**Dispensed:** \_(prescription)

**Initial comments from the submitter (concerns, observations, etc.):** The tradename was submitted with NDA 20-908. Please expedite the review.

filename: 20682.tm

**NOTE:** Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 1993

# Meeting Minutes

**Date:** March 19, 1999      **Time:** 11:00 – 12:30PM      **Location:** Parklawn, 17B-43

**NDA** 20-908      **Drug:** VAGIFEM™ (17-β-Estradiol)      **Indication:** HRT

**Sponsor:** Novo Nordisk Pharmaceuticals

**Type of Meeting:** Labeling (Industry)

**Meeting Chair:** Marianne Mann, MD

**External Lead:** Liz Bloss, Ph.D.

**Meeting Recorder:** Jennifer Mercier

## **FDA Attendees:**

Marianne Mann, MD- Deputy Director, Division of Reproductive and Urologic Drug Products, DRUDP; HFD-580

Ridgely Bennett, M.D. – Medical Officer, DRUDP; HFD-580

Dena Hixon, M.D. – Medical Officer, DRUDP; (HFD-580)

Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)

Amit Mitra, Ph.D. – Chemist, (DNDCII) @ DRUDP (HFD-580)

Edward Nevius, Ph.D. – Director, Division of Biometrics II (DBII; HFD-715)

Lisa Kammerman, Ph.D. – Statistics Team Leader, (DBII; HFD-715) @ DRUDP (HFD-580)

Barbara Elashoff, Ph.D. – Statistician, (DBII; HFD-715) @ DRUDP (HFD-580)

Sam Haidar, Ph.D. – Biopharmaceutics Reviewer, Division of Clinical Pharmacology and Biopharmaceutics (DCPB) @ DRUDP (HFD-580)

Terri Rumble, Chief, Project Management Staff, DRUDP; (HFD-580)

## **External Attendees:**

Dirrit Anderson, M.D., Manager, Regulatory Affairs, Novo Nordisk Pharmaceuticals

Kathryn Batt, Regulatory Affairs, Novo Nordisk Pharmaceuticals

Lieselotte Bloss, D.V.M., Regulatory Affairs, Novo Nordisk Pharmaceuticals

Jeanne Braavig, Ph.D., Regulatory/CMC Manager, Novo Nordisk Pharmaceuticals

Won-Chin Huang, Ph.D., Statistical Director, Novo Nordisk Pharmaceuticals

Kim West Jyrgensen, Ph.D., CMC Production, Novo Nordisk Pharmaceuticals

Ingelise Kvorning, Ph.D., Project Director, Novo Nordisk Pharmaceuticals

Margaret Mazzeo, Statistics, Novo Nordisk Pharmaceuticals

Mary Ann McElligott, Ph.D., Regulatory Affairs, Novo Nordisk Pharmaceuticals

Nayan Nanavati, Associate Director of Development, Novo Nordisk Pharmaceuticals

Barry Reit, M.D., Vice President, Regulatory Affairs, Novo Nordisk Pharmaceuticals

John Whisnant, M.D., Vice President, Development and Research, Novo Nordisk Pharmaceuticals

**Meeting Objective:** To review and finalize labeling and discuss a chemistry issue.

**Discussion:**

Label: See Draft Label

**Chemistry:**

- according to compliance, the excipient site has not been inspected
- the sponsor can provide information supporting the acceptable inspection of the excipient site
- that information will be faxed to compliance

**Decisions made:** See Draft Label

**Unresolved decisions:** Patient Package Insert

**Action Items:**

- Final Label will be faxed Tuesday, March 23, 1999.

/S/

Minutes Preparer

/S/ *MD*  
Concurrence, Chair

3/25/99

cc:

Original IND

HFD-580/DivFile

HFD-580/PM/Rumble/Pauls/Mercier

HFD-580/Rarick/Mann/Bennett/Rhee/Mitra/Kammerman/Elashoff/Parekh/Madani/Haidar/Nevius/Hixon

drafted: March 23, 1999/Mercier

concurrence:

final:

MEETING MINUTES



Novo Nordisk

## Patent Certification

### Vagifem

Novo Nordisk A/S

Novo Allé  
2880 Bagsvaerd  
Denmark

Tel. 4444 8888  
Fax. 4449 0555  
Telex 37173

A/S reg. nr. 16201

Pursuant to CFR 314.53(c)(3), the undersigned declares that there are no patents held by Novo Nordisk A/S which claim Vagifem (25 µg estradiol) or which claim a method of using Vagifem with respect to which a claim of patent infringement could reasonably be asserted against a non-licensed person.

Date: 30 January 1998

By:

Torsten Nørgaard  
Corporate Patents  
Novo Nordisk A/S

EXCLUSIVITY SUMMARY FOR NDA # 20-908 SUPPL # \_\_\_\_\_

Trade Name Vagifem Generic Name 17-β-Estradiol

Applicant Name Novo Nordisk Pharmaceuticals HFD # 580

Approval Date If Known \_\_\_\_\_

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?  
YES / X / NO / \_\_\_ /

b) Is it an effectiveness supplement?  
YES / \_\_\_ / NO / X /

If yes, what type? (SE1, SE2, etc.) \_\_\_\_\_

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")  
YES / X / NO / \_\_\_ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /  / NO /  /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /  / NO /  /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /  / NO /  /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-472 Estring

NDA# 20-847 Esclim

NDA# 20-655 Alora

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /    / NO /    /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /  / NO /  /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /  / NO /  /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

\_\_\_\_\_  
\_\_\_\_\_

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /  / NO /  /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /  / NO /  /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

VAG/PD/9/US

VAG/PD/5/CAN

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.





(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /    /

NO / X /

If yes, explain: \_\_\_\_\_

\_\_\_\_\_

/S/

3/25/99

Signature

Date

Title: Project Manager

/S/

3/25/99

Signature of Office/

Date

Division Director

cc: Original NDA    Division File    HFD-93 Mary Ann Holovac

### PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: <u>20908</u>	Trade Name: <u>VAGIFEM (17-B-ESTRADIOL) VAGINAL TABS</u>
Supplement Number:	Generic Name: <u>17-B-ESTRADIOL</u>
Supplement Type:	Dosage Form: <u>TAB</u>
Regulatory Action: <u>AP</u>	Proposed Indication: <u>HRT</u>

**IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION?**  
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?  
 NeoNates (0-30 Days )  Children (25 Months-12 years)  
 Infants (1-24 Months)  Adolescents (13-16 Years)

Label Adequacy	<u>Does Not Apply</u>
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:  
This product and indication is not applicable to a pediatric population.

Not for pediatric use

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,  
JENNIFER MERCIER

Signature

Date

3/24/99

NDA 20-908  
Vagifem  
Original NDA  
Debarment Statement

Date: March 23, 1999

Final Version  
Page 1

**Novo Nordisk  
Pharmaceuticals Inc.**

### Debarment Statement

Novo Nordisk Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this submission.



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Barry Reit, Ph.D.  
Vice President  
Regulatory Affairs

## Teleconference Minutes

**Date:** March 3, 1999

**Time:** 4:50 - 4:55pm

**Location:** Terri's office

**NDA 20-908**

**Drug:** Vagifem (17-estradiol) vaginal tabs

**Indication:** Estrogen Replacement Therapy

**Sponsor:** Novo Nordisk

**Type of Meeting:** Guidance (information request)

**Meeting Chair:** Ameeta Parekh, Ph.D.

**External Lead:** Liz Bloss

**Meeting Recorder:** Terri Rumble

**FDA Attendees:**

Ameeta Parekh, Ph.D., Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @  
Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)  
Terri Rumble, Chief, Project Management Staff, DRUDP (HFD-580)

**External Attendees:**

Liz Bloss, Novo Nordisk

**Meeting Objective:** To convey the following Biopharmaceutics requests regarding the recent dissolution data to the sponsor:

1. Provide the information to confirm that the Type I formulation used in the recently submitted dissolution data is the same as the clinical/bio batches to enable linking the two formulations. These data are key to link the clinical and to-be-marketed formulations.
2. Provide the individual raw data for all pH media [ ] that was submitted in the submission dated February 24, 1999. Please provide volume/Page # that contain individual raw data for Type I and Type II *in vitro* dissolution in the NDA. (These data can be faxed to expedite the review process.)
3. Provide the F<sub>2</sub> values as defined in the SUPAC IR guidance for similarity to support the information linking the clinical to the actual marketed formulations in different pH media.
4. Provide the electronic files for the dissolution data (include the raw data).

**Action Items:**

- The requests will be addressed as soon as possible by the sponsor, following receipt of the data from Denmark (by March 4 or 5, 1999). Data will be faxed followed by hard copy or electronic copy for review and for the NDA file.

/S/

\_\_\_\_\_  
Minutes Preparer

/S/

\_\_\_\_\_  
Concurrence, Chair

cc:

Original NDA 20-908

HFD-580/DivFile

HFD-580/PM/Rumble/Mercier

HFD-580/Rarick/Mann/Parekh/Haidar/Mandani

drafted: tfr/3.3.99/20908bph.wpd

concurrence: Parekh, 3.4.99

final: Rumble, 3.5.99

MINUTES

Mercier

## Meeting Minutes

**Date:** November 13, 1998      **Time:** 12:00-1:00 PM

**Location:** 17B-43

**NDA:** 20-908

**Drug:** Vagifem

**Indication:** HRT

**Sponsor:** Novo Nordisk Pharmaceuticals

**Type of Meeting:** 6 Month Status Meeting (Internal)

**Meeting Chair:** Ridgley Bennett, M.D.

**Meeting Recorder:** Jennifer Mercier

### FDA Attendees:

Ridgley Bennett, M.D., Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

Amit Mitra, Ph.D., Chemist, DNDCII @ DRUDP (HFD-580)

Barbara Elashoff, Ph.D.- Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Sam Haidar, Ph.D.- Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Soraya Madani, Ph.D.- Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Jennifer Mercier, B.S. - Project Manager, DRUDP (HFD-580)

**Meeting Objective:** To discuss the review status of this pending application.

### Discussion:

- Chemistry, Manufacturing and Controls (CMC)
  - the inspections have not been completed
  - tradename has not been established
- Biopharmaceutics
  - requested that additional information to be submitted electronically
- Clinical
  - the medical officer is aware of the due date for this application and is expected to have it completed on time
- Statistics
  - requested that additional information be submitted electronically
- Toxicology
  - the pharmacologist is aware of the due date for this application and is expected to have it completed on time

**Action Items:**

- request the electronic information the statistician and pharmacokinetics reviewers need to complete their reviews

/S/

Minutes Preparer

/S/

Concurrence, Chair

cc:

Original NDA  
HFD-580/DivFile  
HFD-580/Mercier/Rumble/Pauls/  
HFD-580/Rarick/Mann/Bennett/Jordan/Rhee/Mitra/Haidar/Madani/Parekh/Kammerman/Elashoff

drafted:

concurrence:

final:

MEETING MINUTES



NDA 20-908

Novo Nordisk Pharmaceuticals  
Attention: Barry Reit, Ph.D.  
Vice President, Regulatory Affairs  
100 Overlook Center, Suite 200  
Princeton, NJ 08540-7810

MAR 15 1999

Dear Dr. Reit:

Please refer to your pending May 29, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vagifem (25 ug estradiol) Vaginal Tablets.

We also refer to your submission dated May 28, 1998.

We are reviewing the Chemistry section(s) of your submission and have the following comments and information requests:

Drug Product:

1. The sampling procedure for each test method used to release the drug product should be provided.
2. Based on the recommendation of the Office of Clinical Pharmacology and Biopharmaceutics, the in vitro release rate specifications should be changed as follows:

The specification sheet should be changed to reflect the changes in specification on release and shelf-life.

Stability of the drug product:

1. The specifications for the single unknown impurity and the sum of impurities (total degradation products) were not provided at shelf-life. Specification for those attributes at shelf-life should be provided, otherwise, proper justification should be provided.
2. A shelf-life of three years cannot be supported since the analytical method (for related substances) used to determine this conclusion was semi-quantitative and the dissolution method used is not the current dissolution method. Therefore, a two-year shelf-life is granted based on 12-month stability data at 25C/60%RH and 6-months at 40C/75%RH.

3. A post-approval stability commitment should be provided. For reference, see "Guidance for Industry, Stability Testing of Drug Substances and Drug Products, June 5, 1998."

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

JSI

3/15/99

Moo-Jhong Rhee, Ph.D.  
Chemistry Team Leader, for the  
Division of Reproductive and Urologic Drug  
Products, (HFD-580)  
DNDC II, Office of New Drug Chemistry  
Center for Drug Evaluation and Research

NDA 20-908

Page 3

cc:

Archival NDA 20-908

HFD-580/Div. Files

HFD-580/J.Mercier

HFD-580/Rhee/Mitra/Rarick/Mann

HFD-820/DNDC Division Director (only for CMC related issues)

DISTRICT OFFICE

Drafted by: /March 9, 1999

Initialed by: Rumble/March 11, 1999

final: March 12, 1999

filename: 20908IR.WPD

INFORMATION REQUEST (IR)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

*Markow*

NDA 20-908

Food and Drug Administration  
Rockville MD 20857

JUN 4 1998

Novo Nordisk Pharmaceuticals Inc.  
Attention: Barry Reit, Ph.D.  
Vice President, Regulatory Affairs  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-8710

Dear Dr. Reit:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Vagifem® (estradiol) vaginal tablets  
Therapeutic Classification: Standard  
Date of Application: May 28, 1998  
Date of Receipt: May 29, 1998  
Our Reference Number: 20-908

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 27, 1998 in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Mr. John C. Markow, Project Manager, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

*/S/*

*6/5/98*

Lana L. Pauls, M.P.H.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

NDA 20-908

Page 2

cc:

Original NDA 20-908

HFD-580/Div. Files

HFD-580/CSO/JMarkow

HFD-580/LRarick/MMann/RBennett/LPauls/AJordan/MRhee/ADorantes/KMeaker/GTurner/  
MAskine/SHaidar/AMitra/KRaheja/LKammerman

DISTRICT OFFICE

Drafted by: JMarkow/June 3, 1998

Concurrence:

ACKNOWLEDGMENT (AC)

GENERAL CORRESPONDENCE

March 25, 1999

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: Vagifem™  
NDA 20-908 Final Label

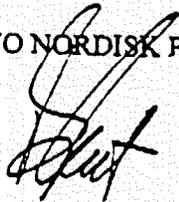
Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem and the request from Jennifer Mercier, today March 25th, 1999 to make minor changes on page 17 and to submit the final label (edition 3/25/99) incorporating all agreed upon comments. Please find the Physician Package Insert (edition 3/25/99) enclosed.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.



Barry Reit, Ph.D.  
Vice President, Regulatory Affairs



Novo Nordisk

Novo Nordisk  
Pharmaceuticals, Inc.

Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

GENERAL CORRESPONDENCE

March 25, 1999

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk

Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Re: Vagifem™  
NDA 20-908 CMC review comments

Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem, the CMC review comments received on March 15, 1999 and your subsequent recommendation. Novo Nordisk accepts your proposal from March 24, 1999 for the specification limits to be:

Please find attached the revised Finished Product Specification for Vagifem to reflect the above changes in specification on release and shelf-life.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

GENERAL CORRESPONDENCE

ORIGINAL

ORIG AMENDMENT

HL

1 24, 1999

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk

Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Re: Vagifem™  
NDA 20-908 CMC review comments

Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem and the CMC review comments received on March 15, 1999 and your subsequent recommendation from yesterday, March 23, 1999. Below please find the outstanding comment and our response. For ease of review we have restated the review comments in italic font.

proposal from yesterday, March 23, 1999 is as follows:  
*in vitro release rate specifications should be changed as follows:*

At the 4 hours sampling point this means that the limits are tightened 10% at both the upper and the lower limit. Novo Nordisk accepts your proposal at the 4 hours limit.

At the 8 hours sampling point you proposed the limits to be tightened 10% at the lower limit and 10% at the upper limit.

The Vagifem tablet is a hydrophilic matrix tablet, where it is a well known phenomenon for these type of matrix tablets that a larger variation in release is observed when the matrix is going to be depleted of drug. This is the case at 8 hours where more than 10% of the drug is released. And this is our reason for requesting a wider range at this sampling point.

The variation in release is larger at 8 hours compared to the variation at 4 and 2 hours which is reflected in the pooled standard deviations (ref. Vol. 1.4 page 81 - 100, "Justification for the Dissolution Specification Limits for Vagifem" and the release data from 25 new batches provided 18 March).

Based on this Novo Nordisk therefore recommends to tighten the previous limits at 8 hours with 10% for both upper and lower limit and propose the following limits: 4 hours: 10%.

Novo Nordisk accepts your proposal at the 4 hours limit.

Therefore our proposal for specification limits is:

This proposal includes that we have tightened both the 4 hours limits and the 8 hours limits equally.

447151

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager  
(987-5852).

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

*Barry Reit for B. Reit*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE

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M1981

GENERAL CORRESPONDENCE

Novo Nordisk

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Novo Nordisk  
Pharmaceuticals,  
Suite 200  
100 Overlook Cent  
Princeton, NJ 085  
Tel. 609-987-5800  
Fax 609-921-8082

March 24, 1999

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Re: Vagifem™  
NDA 20-908 CMC review comments

Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem and the CMC review comments received on March 15, 1999 and your subsequent recommendation from today, March 24, 1999. Below please find the outstanding comment and our response. For ease of review we have restated the review comment in italic font.

Your proposal from today, March 24, 1999 is as follows:  
*The in vitro release rate specifications should be changed as follows:*

We accept your proposal for the specification limits to be:

The specification sheet will be changed to reflect the above changes in specification on release and shelf-life and will be forwarded to you as soon as possible.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager  
(609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

*Mame Ellyott for Barry Reit*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED
GSO APPROVED
<input type="checkbox"/> N.A.I. <input checked="" type="checkbox"/> MEMO
DATE

GENERAL CORRESPONDENCE

ORIGINAL

ORIG AMENDMENT

March 19, 1999

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk

BC

Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Re: Vagifem™  
NDA 20-908 CMC Hillroedgade PAI

Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem and the FDA teleconference today, March 19, 1999. Below please find documentation that may be helpful in substantiating the Hillroedgade QC laboratory for excipients as acceptable. As stated during the teleconference, this site is the only site where excipients are tested.

The site in question was listed in the NDA volume 1.3 page 123. (Attachment 1) The address was given as Novo Nordisk A/S Hilleroedgade 31, DK-2200 Copenhagen. In fact this site has an additional address name, which is Novo Nordisk, Copenhagen (Fuglebakken), Nordre Fasanvej 215, DK-2000 Copenhagen. This address was listed on page 5 of 5 in the correspondence sent to FDA (HFC-133) November 10, 1998 provided in Attachment 2. Novo Nordisk has not heard from the Division of Emergency and Investigational Operations.

This site was inspected in 7/28 - 8/1/97 by James Giefer, FDA. The statement in the EIR, page 22 reads as follows: "No deficiencies noted in laboratory operations." FDA sent a letter to Novo Nordisk on October 27, 1997 indicating that the inspection was "closed". (Attachment 3)

During a discussion on February 24, 1999 with Lieselotte Bloss and Mr. Mestrandrea, the inspector for this site inspection, he indicated that he had been informed during his inspection for Vagifem by HFC-133 that this site was rated as acceptable, based on a previous inspection. He recommended that L. Bloss speak with Gary Pierce. L. Bloss spoke with Marsha Major, who promised to look into this matter.

Additionally, it may be possible that the "Pending Status" is in conjunction with an unrelated Novo Nordisk product located at Brennum Park, DK-3400 Hilleroed which has a similar name. (refer to Attachment 2).

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

*Martin Elliott for Barry Reit*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED
GSO ACTION:
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DETAILS

GENERAL CORRESPONDENCE

Novo Nordisk

ORIGINAL

ORIG AMENDMENT

BC

March 19, 1999

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk  
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Tel. 609-987-5800  
Fax 609-921-8082



Re: Vagifem™  
NDA 20-908 CMC review comments

Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem and the CMC review comments received on March 15, 1999. Below please find the comment and our response. For ease of review we have restated the review comment in italic font.

*Stability of the drug product*

*1. The specification for the single unknown impurity and the sum of impurities (total degradation products) were not provided at shelf-life. Specification for those attributes at shelf-life should be provided, otherwise, propose justification should be provided.*

Previously, Novo Nordisk has suggested the following limits for impurities/degradation products:

6-Keto-E2:            %  
6-Dehydro-E2:        %

The two impurities are dominant degradation products and were selected as stability indicators for the degradation of E2 in Vagifem and included in the specification as specified impurities.

Due to placebo interference in the analysis no limits for "other single impurities" and consequently, no limit for "sum of impurities" were suggested.

The rationale for this specification has been given in the report "Justification of the Specifications for the Content of Related Substances in Vagifem" (NDA Vol. 1.4 page 18 and 64) which includes the evaluation of release limits as well as the calculation of the above mentioned shelf life limit.

Further, the report discuss the difficulties regarding the process of setting up limits for "other single impurities" and "sum of impurities". These difficulties is due to excipient interference in the chromatogram of Vagifem which is connected with the sample preparation procedure of the method - an issue which has been addressed in detail in the validation report "Validation of the Method for the Determination of Degradation products / Chromatographic Impurities in Vagifem 25 µg" (NDA vol. 1.9 page 160).

Besides the excipient interference in the chromatogram, it is our experience that the impurity profile of a placebo may change during storage which also implies uncertainty to the evaluation of whether an unknown peak originates from estradiol or placebo.

Based on these observations regarding excipient interference in the analytical method it has been difficult to set up adequate shelf life limits for unknown impurities and consequently a limit for "sum of impurities".

However, in connection with the review of the Vagifem NDA, FDA has now requested Novo Nordisk to provide such limits.

Even though 6-Keto-E2 and 6-Dehydro-E2 are primary degradation products (the former being the dominant one) the impurity profile of Vagifem contain other impurities. Appendix A in above mentioned justification report shows that some batches contains Estrone (primarily an impurity of synthesis) and Appendix B in the same report demonstrates that a whole range of degradation products are formed when the Vagifem is subjected to very accelerated storage conditions.

Taking into consideration the uncertainty introduced by the excipient interference as well as the limited experience regarding batch to batch variation using the method Novo Nordisk suggest the following shelf life limits including limits for "other single impurities" and "sum of impurities":

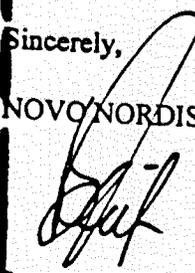
6-Keto-E2:	%
6-Dehydro-E2:	%
"other single impurities":	%
"sum of impurities":	%

The limit of 1.0% for "other single impurities" correspond to the threshold value for identification of degradation products given in the ICH Harmonised Tripartite Guideline concerning Impurities in New Medicinal Products. The limit of 4.0% for "sum of impurities" reflects the limits for the two specified impurities and the limit for "other single impurities" plus a contribution from "Related substances total" in estradiol hemihydrate ( limit  $\leq 1.0\%$ ).

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

  
Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

GENERAL CORRESPONDENCE

Novo Nordisk

ORIGINAL

ORIG AMENDMENT

BC

March 18, 1999

Dr. Lisa Rarick  
 Director, Division of Reproductive and  
 Urologic Drug Products, HFD 580  
 Office of Drug Evaluation II  
 Center for Drug Evaluation & Research  
 Food & Drug Administration  
 5600 Fishers Lane  
 Rockville, MD 20857



Novo Nordisk  
 Pharmaceuticals, Inc.  
 Suite 200  
 100 Overlook Center  
 Princeton, NJ 08540-7810  
 Tel. 609-987-5800  
 Fax 609-921-8082



Re: Vagifem™  
 NDA 20-908 CMC review comments

Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem and the CMC review comments received on March 15, 1999. Below please find the comments and our responses. For ease of review we have restated the review comments in italic font.

**Drug Product:**

1. *The sampling procedure for each test method used to release the drug product should be provided.*

The sampling procedure for in-process control of granulation and compression is stated in "Manufacturing process" in the NDA Vol.1.3 page 127.

The sampling procedure for each test method used to release the drug product is given in the table below.

Test	Sample size	Sampling Interval
Identification (E2)	2 x 10 coated tablets 30 coated tablets	1 per batch
Content uniformity (E2)	30 coated tablets*	1 per batch
Assay (E2)	2 x 10 coated tablets	1 per batch
Related substances	12 coated tablets	1 per batch
Dissolution	6 coated tablets **	1 per batch
Loss on drying	30 coated tablets	1 per batch
Appearance	10 coated tablets	1 per batch
Ps. Aeruginosa	10 g of coated tablets	1 per batch
Enterobacteria	10 g of coated tablets	1 per batch
S. aureus	10 g of coated tablets	1 per batch
Aerobic bact. and fungi	10 g of coated tablets	1 per batch

REVIEWS COMPLETED

\* Level 1 : 10 tablets  
 Level 2 : 20 tablets  
 \*\* Level 1 : 6 tablets  
 Level 2 : 6 tablets  
 Level 3 : 12 tablets

CSO ACTION:  
 LETTER  N.A.I.  MEMO  
 CSO INITIALS \_\_\_\_\_ DATE \_\_\_\_\_

2. Based on the recommendation of the Office of Clinical Pharmacology and Biopharmaceutics, the in vitro release rate specifications should be changed as follows:

*The specification sheet should be changed to reflect the changes in specification on release and shelf-life.*

The dissolution limits proposed in the NDA are justified in report PD-970882 in Vol. 1.4 page 82-100. The same report is referred to in Vol. 1.13 page 211 - 229. The justification in this report is based on 17 production scale batches. Since the justification report was made 25 additional batches have been produced for our existing market outside the US. Dissolution data from these 25 batches are provided in Attachment 1. The list shows 38 data sets of 6 tablets as some of the batches were tested on L2 using 12 tablets. The bold figures show all the values which will not comply with the L1 limits proposed by FDA. Two out of the 38 data set will comply with the limits proposed by FDA on L1. Comparing the average values after 3, 5 and 10 hours for the 25 new batches with the averages values for the batches shown in report PD-970882 page 216 and 218 it is clear that the dissolution data from the 25 new batches support the previous justification for dissolution limits. From the average values 33% after 3 hours and 54 % after 5 hours it is seen that the intervals proposed by FDA is placed non symmetrically around the average. From the graphs showing minimum, maximum and average values at 3 - 5 and 10 hours respectively it is seen how the values are distributed within the proposed limit from FDA and our previously proposed limits. We therefore recommend to maintain the dissolution limits proposed in the NDA.

#### *Stability of the drug product*

1. *The specification for the single unknown impurity and the sum of impurities (total degradation products) were not provided at shelf-life. Specification for those attributes at shelf-life should be provided, otherwise, propose justification should be provided.*

We are currently preparing a response to your comments.

2. *A shelf-life of three years cannot be supported since the analytical method (for related substances) used to determine this conclusion was semi-quantitative and the dissolution method used is not the current dissolution method. Therefore, a two year shelf-life is granted based on 12-month stability data at 25°C/60%RH and 6-months at 40°C/75%RH.*

A shelf-life of two years based on 12-month stability data at 25°C/60%RH and 6-months at 40°C/75%RH is accepted.

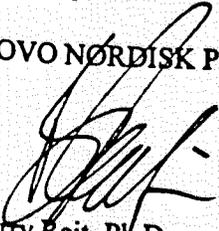
3. *A post-approval stability commitment should be provided. For reference see "Guidance for Industry, Stability of Drug Substances and Drug Products, June 5, 1998"*

The three NDA stability batches are production batches. 12 month data were submitted to the FDA January 14, 1999. The study will continue for 48 months with reporting after 24, 36 and 48 months. A commitment for stability studies post-approval is provided in Attachment 2.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

  
Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

NDA AMENDMENT  
SAFETY UPDATE

Novo Nordisk

ORIGINAL

~~QTD AMENDMENT~~

SV

February 26, 1998



Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

noted  
3/3/99  
RAB

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: NDA 20-908 Vagifem

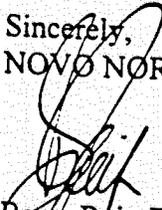
Dear Dr. Rarick:

Reference is made to NDA 20-908 for Vagifem<sup>®</sup>, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and the request from the medical reviewer for a Safety Update, transmitted by Jennifer Mercier on February 22, 1999.

Attached please find the safety update of adverse events for Vagifem reported from September 29, 1998 through February 25, 1999.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Manager, Regulatory Affairs at (609) 987-5852.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

  
Barry Reit, Ph. D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE

GENERAL CORRESPONDENCE

BB  
ORIG AMENDMENT

February 24, 1999

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk

ORIGIN

~~NEW CORRE~~

NE

Novo Nordisk  
Pharmaceuticals, Inc.

Suite 200  
100 Overlook Center  
Princeton, NJ 08540-781  
Tel. 609-987-5800  
Fax 609-921-8082

Re: **Vagifem™**  
**NDA 20-908**  
**Dissolution Report**

Dear Ms. Mercier:

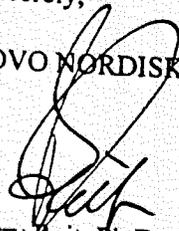
Reference is made to NDA 20-908 for Vagifem®, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and to the biopharmaceutics reviewer's comments (1/13/99 fax) and our subsequent proposal for obtaining additional dissolution data (1/15/99 fax).

Enclosed please find our February 22, 1999 report, "Dissolution of Vagifem® measured at different pH values". For ease of review, we have also included the January 15, 1999 testing proposal and information which was approved by the FDA on January 25, 1999. These reports were also faxed to you on February 24, 1999.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

  
Barry Keit, Ph.D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
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CSO INITIALS
DATE

GENERAL CORRESPONDENCE

January 14, 1999

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



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Novo Nordisk  
Pharmaceuticals, Inc.  
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Tel. 609-987-5800  
Fax 609-921-8082

Re: Vagifem™  
NDA 20-908

Dear Ms. Mercier:

Reference is made to NDA 20-908 for Vagifem, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and your recent requests (12/28/98 and 1/6/99) for additional information.

Enclosed please find the following analytical assay validation reports for VAG/PD/10/USA as requested by the Biopharm reviewer:

Estradiol: The validation reports are located in volume 1.16, pages 1-79 of NDA 20-908.  
Estrone: "Validation of and Serum" (provided in Attachment 1) for the Analysis of Estrone (F1) in Human Plasma  
FSH: "FSH-Chemiluminescence Assay, Assay Validation" (provided in Attachment 2).

For VAG/PD/4/S, the validation report for Estradiol is located in NDA volume 1.13, page 121. Validation reports for Estrone and FSH for VAG/PD/4S are not available. This study was performed in 1988/89 and validation reports for the secondary endpoints were not provided.

Additionally, please find enclosed the requested stability data in Attachment 3, "12 Months Interim Report on Vagifem®".

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

ORIGINAL  
GENERAL CORRESPONDENCE

NEW CORRESP

Novo Nordisk

C

January 13, 1999

AT 1/27/99

Novo Nordisk  
1/21/99



Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

AT 1/22/99

Novo Nordisk  
1-27-99

Re: Vagifem™  
NDA 20-908

Dear Ms. Mercier:

Reference is made to NDA 20-908 for Vagifem, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and your request of 1/13/99 regarding the pre-NDA meeting package for the Medical Officer.

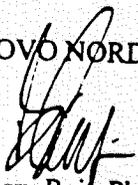
Please find enclosed one copy of the April 7, 1997 IND NDA Meeting Information Package".

Amendment Serial No. 036, "Clinical Pre

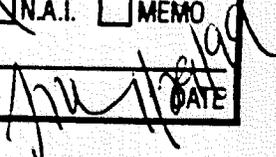
If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

  
Barry Reit, Ph.D.  
Vice President,  
Regulatory Affairs



REVIEWS COMPLETED
CSO ACTION:
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CSO INITIALS  DATE

ORIGINAL  
GENERAL CORRESPONDENCE

NEW CORRESP

January 7, 1999

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: Vagifem™  
NDA 20-908



Novo Nordisk

Novo Nordisk  
Pharmaceuticals, Inc.

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100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Dear Ms. Mercier:

Reference is made to NDA 20-908 for Vagifem, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and your request of January 6, 1999 for information.

Please find enclosed 2 Desk Copies of the ISS and ISE sections and a electronic copy of the Annotated Physician Package Insert (AnnotPI.doc; MS Word 95 format). We also are including Zip files on disk of the Patient Package Insert and the Physician Package Insert.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

GENERAL CORRESPONDENCE

December 10, 1998

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: Vagifem™  
NDA 20-908

Dear Ms. Mercier:

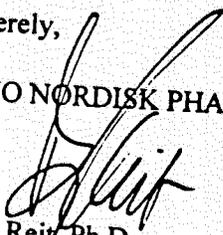
Reference is made to NDA 20,908 for Vagifem, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and your recent request for information for the Statistical Reviewer.

Please find enclosed 2 disks containing Excel Workbook Files of data for studies 5/CAN, 9/USA and 033/ATR. Also attached are paper copies of the first page of each sheet in each of the workbooks, documentation of the variable names and formulas and/or explanations of all derived variables as required.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.



Barry Reit, Ph.D.  
Vice President, Regulatory Affairs



Novo Nordisk

Novo Nordisk  
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ORIGINAL

GENERAL CORRESPONDENCE

Novo Nordisk



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December 7, 1998

NU

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
6600 Fishers Lane  
Rockville, MD 20857

Re: Vagifem™  
NDA 20-908

Dear Ms. Mercier:

Reference is made to NDA 20,908 for Vagifem, an estrogen product for the relief of atrophic vaginitis due to estrogen deficiency and your recent request for information for the Biopharm Reviewer.

Please find enclosed 2 disk copies and 2 paper copies of the raw data for the individual subjects in Excel spreadsheets for Vagifem studies 6/ABS (4/S) and 10/USA. These studies represent the primary source of pharmacokinetic data in this NDA. Please advise if Novo Nordisk should furnish additional data from pilot or secondary studies.

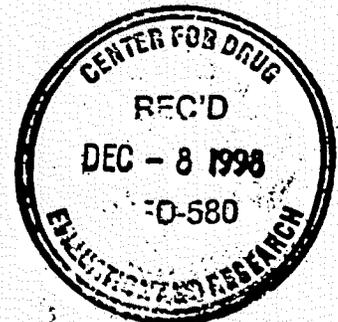
If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

Sincerely,

NOVONORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____



GENERAL CORRESPONDENCE

Novo Nordisk



BB  
ORIG AMENDMENT

November 25, 1998

Jennifer Mercier  
CSO, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Re: Vagifem™  
NDA 20-908

Dear Ms. Mercier:

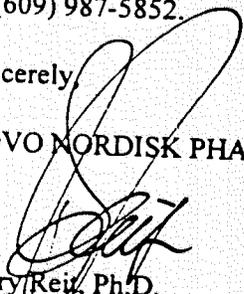
Reference is made to NDA 20,908 for Vagifem, and your recent request for information for the Biopharmaceutical Reviewer.

Please find enclosed on disk (Word for Windows Version 7) the electronic version of the Overall Summary of Human Pharmacokinetics and Bioavailability, Individual Study Report Summaries and the Annotated Package Insert. Additionally, the reviewer asked for the raw data for the individual subjects in Excel spreadsheets. This information will be forwarded to you during the second week of December.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Regulatory Affairs Manager at (609) 987-5852.

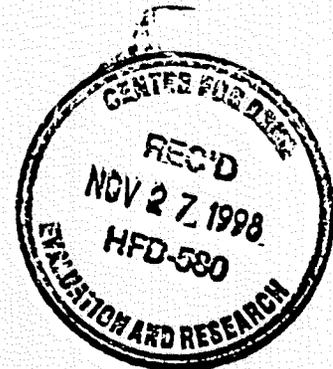
Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

  
Barry Reij, Ph.D.  
Vice President, Regulatory Affairs

/albr

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS
DATE



NDA Amendment

October 22, 1998

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk

Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

Re: NDA 20-908 Vagifem® 25 µg Estradiol Vaginal Tablets

Dear Dr. Rarick:

Reference is made to NDA 20-908 Vagifem® 25 µg Estradiol Vaginal Tablets.

Pursuant to 21CFR 314.60 we are submitting in triplicate, an amendment to the Chemistry, Manufacturing and Controls section to reflect changes made in several items since submission of the referenced document.

These changes are minor in nature and consist of editorial changes, name changes, changes due to compendial methods, new model of equipment, supplier changes, etc.. An incorrect method of analysis (A 3302a), inadvertently submitted, is being replaced with the correct method ("Identification of plastic foils as film by FTIR", A3537a). Descriptions of the changes, along with supporting documentation have been provided, including the NDA location of affected documents. (Attachment 1)

We trust these changes will not affect the review clock.

Should you have any questions, please contact Lieselotte Bloss, DVM, Manager, Regulatory Affairs at (609) 987-5852.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

cc: FDA Field copy and certification

DUPLICATE

120 DAY SAFETY UPDATE

Novo Nordisk

ORIG AMENDMENT  
SU



Novo Nordisk  
Pharmaceuticals, Inc.  
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

October 21, 1998

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

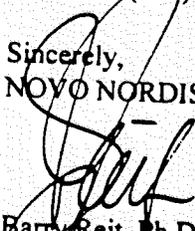
Re: **NDA 20-908 Vagifem® 25 µg Estradiol Vaginal Tablets**

Dear Dr. Rarick,

Reference is made to the original NDA 20-908 submitted on May 28, 1998 and to 21CFR 314.50, Subpart B (5)(vi)(b). In this update, the status of safety information is reviewed for the time period of April 1, 1998 (cut-off date of March 31, 1998) to September 28, 1998. In the NDA submission cover letter it was indicated that a 12 month stability report would be issued in the 120 day safety update. Since the 12 month sample will not be taken until October 1998, the interim report will not be available until December 1998.

If you need further information, please contact Lieselotte Bloss, DVM, Manager, Regulatory Affairs at (609) 987-5852.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

  
Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

ORIGINAL

Novo Nordisk

*Noted  
7/15/98  
Res*



Novo Nordisk  
Pharmaceuticals Inc.

Suite 200  
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Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

July 9, 1998

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

NEW CORRESP

Re: NDA 20-908, (17-β- estradiol)

REVIEWS COMPLETED	
CSO ACTION:	
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<input type="checkbox"/> MEMO	
<i>Shumble</i>	<i>7/22/98</i>
CSO INITIALS	DATE

*mta  
Dit. V  
7-21-98*

Dear Dr. Rarick:

Novo Nordisk Pharmaceuticals Inc. is herewith resubmitting Form 356h incorporating the corrected indication for NDA 20-908 also described in the Physician Package Insert as requested by John Markow, CSO, on July 8, 1998.

Questions or comments regarding this application should be directed to Lieselotte Bloss, DVM Manager, Regulatory Affairs, at 609/987-5852.

Sincerely yours,

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

*Nda  
KR  
7/21/98*

ORIGINAL NEW DRUG APPLICATION

May 28, 1998

Dr. Lisa Rarick  
Director, Division of Reproductive and  
Urologic Drug Products, HFD 580  
Office of Drug Evaluation II  
Center for Drug Evaluation & Research  
Food & Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk

Novo Nordisk  
Pharmaceuticals Inc.

Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810

Tel. 609-987-5800  
Fax 609-921-8082

Re: NDA 20-908, (17- $\beta$ - estradiol)

Dear Dr. Rarick:

Novo Nordisk Pharmaceuticals Inc. (NNPI) is herewith submitting an original NDA for Vagifem<sup>®</sup>, estradiol vaginal tablets, for the relief of postmenopausal atrophic vaginitis due to estrogen deficiency.

Critical efficacy and safety data are provided in five studies conducted in North America and three supportive studies conducted in Europe. The North American studies are identified as those that provide substantial evidence of efficacy and safety (primary or pivotal studies) and the European studies are deemed as supportive. This was discussed and agreed upon with the Agency at the pre-NDA meeting held on April 29, 1997. Details about key Agency interactions regarding the clinical data in this NDA appear in Item 2, Application Summary (specifically the Clinical and Statistical Data Summary) and in the Reviewer's Guide for Item 8, Clinical Data.

This NDA contains six months stability data as agreed upon with the Division subsequent to communications that took place in November and December, 1997 and January 1998. Full details about stability testing appear in Item 3, Chemistry, Manufacturing and Controls Section (specifically Volumes 5 and 6). At the time of the 120-day safety update, the final stability report will be submitted.

This application is being filed in duplicate (FDA archive copy and technical review copies). For each technical review section, a copy of Volume 1 of the NDA is provided. This volume contains various administrative documents, the NDA Index and the Application Summary. Novo Nordisk Pharmaceuticals Inc. is also providing directly to the Division the field copy of the Item 3, Chemistry, Manufacturing and Controls section. A certification for the Field Copy appears in Volume 1 of the NDA.

NNPI has also placed a reviewer's guide in most sections. The reviewer's guide contains useful background or introductory information including Agency contact information. Additionally, for most items, there is a duplicate Item Table of Contents provided for the use of the reviewer. This additional Table of Contents is contained in a plastic sleeve for easy pull-out use.

Following this letter is FDA Form 356h and the User Fee Cover Sheet. The User Fee will be wired tomorrow, May 29<sup>th</sup>, 1998.

Questions or comments regarding this application should be directed to Lieselotte Bloss, DVM Manager, Regulatory Affairs, at 609/987-5852.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Barry Reit".

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs