CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-907/S-001

Trade Name: Activelle 1mg/0.5mg Tablets

Generic Name: estradiol / norethindrone acetate

Sponsor: Novo Nordisk

Approval Date: November 3, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-001

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	
CSO Labeling Review(s)	
Medical Officer Review(s)	
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-001

APPROVAL LETTER

NDA 20-907/S-001

NOV -3 1999

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

Dear Barry Reit:

Please refer to your supplemental new drug application dated July 8, 1999, received July 9,1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activelle™ (estradiol /norethindrone acetate) 0.5mg/1mg tablets.

We acknowledge receipt of your submission dated August 17, 1999.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for an Analytical Testing Site Change. Your submission stated second quarter 1999, as the implementation date for the change.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Dornette Spell-LeSane, Project Manager, at (301) 827-4260.

Sincerely,

11/2/99

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

cc:
Archival NDA 20-907
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Rarick/Slaughter/Price/Boal/Jordan/Rumble/Rhee/Parekh
HFD-095/DDMS-IMT
~~HFD-820~~/DNDC Division Director
DISTRICT OFFICE

Drafted by: DSL/November 2, 1999
Initialed by:Rumble, 11.2.99, Boal, 11.2.99, Rhee, 11.2.99, Rarick, 11.3.99
final:Spell-LeSane, 11.3.99
filename: 20907.DOC

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-001

CHEMISTRY REVIEW(S)

OCT 21 1999

CHEMIST REVIEW
OF SUPPLEMENT

1. **ORGANIZATION:** CDER/HFD-580 Division of Reproductive and Urologic Drug Products

2. **NDA NUMBER:** 20-907

3. **SUPPLEMENT NUMBERS/DATES:** SCM-001

Letterdate: July 8, 1999
Stampdate: July 9, 1999

4. **AMENDMENTS/REPORTS/DATES:** SNC

Letterdate: August 17, 1999
Stampdate: August 18, 1999

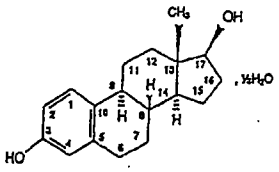
5. **RECEIVED BY CHEMIST:** October 5, 1999

6. **APPLICANT NAME AND ADDRESS:** Novo Nordisk Pharmaceuticals Inc.
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

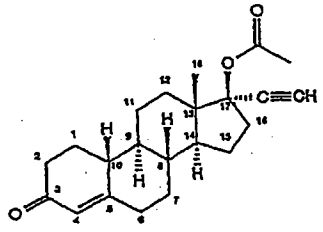
7. **NAME OF DRUG:** Activelle

8. **NONPROPRIETARY NAME:** Estradiol, USP / Norethindrone Acetate, USP

9. **CHEMICAL NAME/STRUCTURE:** Estra-1,3,5(10)-triene-3, 17β-diol



17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate



10. **DOSAGE FORM(S):** Tablets

11. **POTENCY:** 0.5mg Estradiol / 1mg Norethindrone Acetate

12. **PHARMACOLOGICAL CATEGORY:** Estrogen / Progestin

13. **HOW DISPENSED:** Rx

14. RELATED IND/NDA/DMF: NDA # 21-103

15. SUPPLEMENT PROVIDES FOR: Moving QC- Testing Laboratories from current facilities in sites Soeborg and Bagsvaerd to a new facility in site Maaloev.

16. COMMENTS:

This supplement is submitted as Changes Being Effected according to the Guidance for Industry PAC-ATLS per agreement by Nancy Sager on May 21, 1999. The supplement affects Activelle™ (NDA 20-907) and Vagifem® NDA 20-908 as well as Activelle™ (NDA 21-103 for Osteoporosis). Novo Nordisk plans to move the QC-Testing Laboratory ——— , from the current facilities in sites Soeborg and Bagsvaerd to a new facility located under Site Maaloev in Q2 1999. The testing responsibilities for ——— , are testing of active ingredients, drug products and primary packaging materials. These tests will be performed in the new facility under identical conditions as done previously which entails the followings:

The same analytical equipment as previously will be used. It will be requalified after transfer.
The same technicians and chemists as previously will perform the analysis.
The same analytical methods and SOP's will be used as previously.

The table below identifies the names and addresses of the current and new testing site as well as a description of the testing to be performed.

Department	Current Facility Name /Address	New facility Name / Address	Activity
PSM Quality Control ———	Novo Nordisk A/S Novo Alle, ——— DK-2880 Bagsvaerd	Novo Nordisk A /S Novo Nordisk Park, ——— Dk-2760 Maaloev	Physical testing of Primary packaging materials
PSM Quality Control ———	Novo Nordisk A/S Sydmarken 5. ——— DK-2860 Soeborg	Novo Nordisk A/S Novo Nordisk Park, ——— DK-2760 Maaloev	Testing of Drug substance and drug product

A request had been forwarded to EER by Dr. David T. Lin . The EER was returned with an acceptable recommendation on 23 September 1999 (see attachment).

17. CONCLUSIONS AND RECOMMENDATIONS: The supplement may be approved.
Issue approval letter.

18. REVIEWER NAME Jila Boal, Ph. D.

SIGNATURE Jila Boal

DATE COMPLETED October 21, 1999

cc: Original: Division File
HFD-580/JBoal/MRhee/DSpell-LeSane
HFD-510/SMarkofsky
INIT 10/21/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-001

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 20907/001**
Stamp: **09-JUL-1999** Regulatory Due: **09-NOV-1999**
Applicant: **NOVO NORDISK**
100 OVERLOOK CENTER STE 200
PRINCETON, NJ 08540

Priority: **4S** Org Code: **580**
Action Goal: District Goal: **05-OCT-1999**
Brand Name: **ACTIVELLE(ESTRADIOL 1MG/NORETHINDRONATE**
Established Name:
Generic Name: **ESTRADIOL 1MG/NORETHINDRONATE ACETATE 0.**
Dosage Form: **AER (AEROSOL)**
Strength: **1 MG/0.5 MG**

FDA Contacts:

D. SPELL LESANE	**(HFD-580)**	**301-827-4260**	**, Project Manager**
D. LIN	**(HFD-580)**	**301-827-4230**	**, Review Chemist**
M. RHEE	**(HFD-580)**	**301-827-4237**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 23-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: **9613235**
NOVO NORDISK A/S
NOVO NORDISK PARK
MAALEOV, , DA DK-2760

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **23-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE RELEASE TESTER

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20907/001
Stamp: 09-JUL-1999
Regulatory Due: 09-NOV-1999
Applicant: NOVO NORDISK
100 OVERLOOK CENTER STE 200
PRINCETON, NJ 08540
Priority: 4S
Org Code: 580

Action Goal:
District Goal: 05-OCT-1999
Brand Name: ACTIVELLE(ESTRADIOL 1MG/NORETHINDRONATE
Estab. Name:
Generic Name: ESTRADIOL 1MG/NORETHINDRONATE ACETATE 0.

Dosage Form: (AEROSOL)
Strength: 1 MG/0.5 MG

Application Comment: THIS SUPPLEMENT IS FOR A QC TESTING SITE CHANGE. IT IS BUNDLED WITH NDA 21-103 AND NDA 20-908/S-001. (on 23-SEP-1999 by D. LIN (HFD-580) 301-827-4230)

FDA Contacts:
D. SPELL LESANE (HFD-580) 301-827-4260 , Project Manager
D. LIN (HFD-580) 301-827-4230 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 23-SEP-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9613235
NOVO NORDISK A/S
NOVO NORDISK PARK
MAALEOV, , DA DK-2760

DMF No:
AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER
Profile: CTL
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	23-SEP-1999				LINDAV
OC RECOMMENDATION	23-SEP-1999			ACCEPTABLE BASED ON FILE REVIEW	EGASM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-001

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-907/S-001

Novo Nordisk Pharmaceuticals Inc.
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

JUL 13 1999

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

Dear Dr. Reit:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Activelle

NDA Number: 20-907

Supplement Number: S-001

Date of Supplement: July 8, 1999

Date of Receipt: July 9, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 9, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

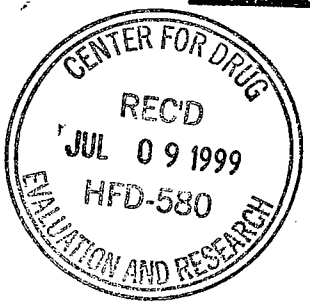
Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ORIGINAL

SUPPLEMENT - CBE

NDA NO. 20907 REF. NO. SCM-001

NDA SUPPL FOR Manufacture



Novo Nordisk

Novo Nordisk Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

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

July 8, 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: Changes Being Effected Supplement for CMC QC Testing Site Change
Bundling of: Activelle™, NDA 20-907
Vagifem®, NDA 20-908

Dear Dr. Rarick:

In March Dr. Susan Lange spoke with Lieselotte L. Bloss, DVM, Asst. Dir. Regulatory Affairs regarding the QC Testing Site Change in reference to NDA 20-907 for Activelle™ approved on November 18, 1998 and NDA 20-908 for Vagifem® approved on March 26,1999. At that time she suggested that we present to Nancy Sager information relevant to the Guidance for Industry PAC-ATLS: Postapproval Changes, April 1998 and request agreement from FDA to submit information as a changes being effected supplement. This request was made and granted by Nancy Sager on May 21, 1998. A copy has been provided in Attachment 1. Since the CBE supplement affects both Activelle and Vagifem we are submitting the pertinent information to the Division of Reproductive and Urologic Drug Products, HFD 580 to be bundled. Copies for both NDA 20-907 and NDA 20-908 are being provided for archival purposes.

In an effort to consolidate production and testing to product specific locations Novo Nordisk expects to move QC-Testing Laboratory (———), from the current facilities in sites Soeborg and Bagsvaerd to a new facility located under Site Maaloev in Q2 1999.

For Activelle and Vagifem the QC-laboratory (———) has performed some of the testing of the active ingredients, drug products and primary packaging materials for several years. QC (———) will continue this testing in the new facility under identical conditions as done previously.

Please note that:

- The same analytical equipment as previously will be used. It will be requalified after transfer.
- The same technicians and chemists as previously will perform the analysis.
- The same analytical methods and SOP's will be used as previously.
- The only difference is the building, which has been constructed specifically for that purpose.

see Review
J.H. Beal
11/3/99

A table identifying the names and addresses of the current and new testing site as well as a description of the testing to be performed is shown below. For location in relevant NDAs please refer to Attachment 2.

Activelle and Vagifem Quality Control Facilities

Department	Current facility Name/Address	New facility Name/Address	Activity
PSM Quality Control	Novo Nordisk A/S Novo Allé, DK-2880 Bagsvaerd	Novo Nordisk A/S Novo Nordisk Park, DK-2760 Maaloev	Physical testing of Primary packaging materials
PSM Quality Control	Novo Nordisk A/S Sydmarken 5, DK-2860 Soeborg	Novo Nordisk A/S Novo Nordisk Park DK-2760 Maaloev	Testing of Drug substance and drug product

The Guidance for Industry PAC-ATLS allows sponsors to make postapproval changes as Changes Being Effected providing the new testing site meets four criteria discussed below:

(1) "The test methods approved in the application or methods that have been implemented under 21CFR 314.70 are used."

The testing of drug substances and drug products and the testing of primary packaging materials performed at the current testing facilities in Soeborg and Bagsvaerd respectively will be transferred to Maaloev and the analytical methods will remain unchanged by the transfer. Please refer to Attachment 3.

(2) *"All post approval commitments made by the applicant relating to the test method(s) have been fulfilled."*

We have not yet been requested to provide Methods Validation Samples by FDA as Vagifem was just approved on March 26, 1999. No other postapproval commitments were made for Vagifem.

cc:
Original NDA 20-907/S-001
HFD-580/Div. Files
HFD-580/CSO/Spelllesane

SUPPLEMENT ACKNOWLEDGEMENT

(3) *"The new testing facility has the capability to perform the intended testing."*

The same analytical equipment as previously will be used. It will be requalified after transfer. The same technicians and chemists as previously will perform the analysis. The same analytical methods and SOP's will be used as previously. The only difference is the building, which has been constructed specifically for that purpose. Please see Attachment 4.

(4) *"The new testing facility has had a satisfactory current good manufacturing (cGMP) inspection within the past 2 years."*

The new testing facility will be a new building on site Maaloev that has had a satisfactory cGMP inspection within the past two years. An establishment inspection for Activelle was conducted at Novo Nordisk's pharmaceutical manufacturing and testing sites in Soeborg, Maaloev and Gentofte, Denmark from February 18 to March 5, 1998 by FDA with an acceptable rating. During this inspection the testing facility in Soeborg was inspected.

An establishment inspection for Vagifem was conducted at Novo Nordisk's pharmaceutical manufacturing sites in Maaloev and Bagsvaerd, Denmark from September 28 to October 2, 1998 by FDA with an acceptable rating.

Consequently, the testing laboratory in terms of analytical equipment, instructions, SOP's and personnel has received and passed a GMP inspection by FDA. The physical lay-out of the new testing facility has not been inspected, because it has recently been built for this purpose. However, it belongs under Site Maaloev which has already been FDA inspected as mentioned above.

Supporting Documentation

The guideline asks for a full description of the testing to be performed by the new facility. We consider that reference to the NDA methods for testing, that remain unchanged, to be adequate.

Please let us know if any additional information is needed to be submitted to the review division. We look forward to hearing from you.

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

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

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

REVIEWS COMPLETED

CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO

AP 11/3/99

CSO INITIALS DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Novo Nordisk Pharmaceuticals Inc.	07/08/99
TELEPHONE NO. *(Include Area Code)* (609) 987-5800	FACSIMILE (FAX) Number *(Include Area Code)* (609) 987-3916
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 100 Overlook Center, Suite 200 Princeton, NJ 08540-7810	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-907

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
estradiol/norethindrone acetate	Activelle

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
estra-1,3,5(10)-triene,5, 17B-diolhemihydrate 17B-acetoxy-19-nor-17a-pregn-4-en-20-yn-3-one

CODE NAME *(If any)*
Kliogest Low Dose

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	1mg NETA/.5mg E2 1mg E2 /0.5mg NETA	Oral

(PROPOSED) INDICATION(S) FOR USE:
Indicated for use in the treatment of moderate to severe vasomotor symptoms associated with the menopause and in the treatment of vulvar and vaginal atrophy, in women with an intact uterus.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Bundling of Changes Being Effected Supplementfor CMC QC Testing Site Change

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

IND 38,483

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Novo Nordisk Pharmaceuticals Inc.	07/08/99
TELEPHONE NO. *(Include Area Code)* (609) 987-5800	FACSIMILE (FAX) Number *(Include Area Code)* (609) 987-3916

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA-20-908

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* 17-B estradiol

PROPRIETARY NAME *(trade name)* IF ANY Vagifem

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
estra-1,3,5 (20)-triene-3, 17B-diol hemihydrate

CODE NAME *(If any)*

DOSAGE FORM: Vaginal tablets

STRENGTHS: 25 of estradiol

ROUTE OF ADMINISTRATION: Vaginal Application

(PROPOSED) INDICATION(S) FOR USE:
Vagifem is indicated for use in the treatment of atrophic vaginitis, a component of urogenital syndrome associated with the estrogen deficiencey of menopause.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Bundling of Changes Being Effected Supplement for CMC WQC Testing Site Change

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

IND 38,483
DMF Numbers 4684, 3829, 5654, 12521, 8593, 12533

GENERAL CORRESPONDENCE

ORIGINAL

~~NEW CORRESP~~
~~SUPPL~~ NEW CORRESP
SNC 001

August 17, 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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 18 1999
HFD-580

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

Re: S-001
Changes Being Effected Supplement for CMC QC Testing Site Change
Bundling of: Activelle™, NDA 20-907
Vagifem®, NDA 20-908

Dear Dr. Rarick:

This correspondence is a note to the file for S-001 to NDA 20-907 (Activelle) and NDA 20-908 (Vagifem). Please note that this supplement has also been submitted to NDA 21-103 currently under review in HFD-580 for the indication of Osteoporosis.

Please find attached a copy of the cover letter sent to Dr. Sobel regarding the submission of the above CBE to the NDA 21-103

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

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

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

REVIEWS COMPLETED
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
AP 11/8/99
CSO INITIALS DATE

see Review
J.H. Sobel
11/3/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Novo Nordisk Pharmaceuticals Inc.	08/17/99
TELEPHONE NO. *(Include Area Code)* (609) 987-5800	FACSIMILE (FAX) Number *(Include Area Code)* (609) 987-3916
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 100 Overlook Center, Suite 200 Princeton, NJ 08540-7810	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-907

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
estradiol/norethindrone acetate	Activelle

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
estra-1,3,5(10)-triene,5, 17B-diolhemihydrate 17B-acetoxy-19-nor-17a-pregn-4-en-20-yn-3-one

CODE NAME *(If any)*: Kliogest Low Dose

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	1mg NETA/.5mg E2	Oral

(PROPOSED) INDICATION(S) FOR USE:
Indicated for use in the treatment of moderate to severe vasomotor symptoms associated with the menopause and in the treatment of vulvar and vaginal atrophy, in women with an intact uterus.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION Bundling of Changes Being Effected Supplementfor CMC QC Testing Site Change

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

IND 38,483

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PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA-20-908

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
17-B estradiol	Vagifem

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
estra-1,3,5 (20)-triene-3, 17B-diol hemihydrate	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Vaginal tablets	25 of estradiol	Vaginal Application

(PROPOSED) INDICATION(S) FOR USE:
Vagifem is indicated for use in the treatment of atrophic vaginitis, a component of urogenital syndrome associated with the estrogen deficiencey of menopause.

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REASON FOR SUBMISSION Bundling of Changes Being Effected Supplement for CMC WQC Testing Site Change

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IND 38,483
DMF Numbers 4684, 3829, 5654, 12521, 8593, 12533