CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-907/S-007

Trade Name:	Activella 1mg/0.5mg Tablets
Generic Name:	estradiol / norethindrone acetate
Sponsor:	Novo Nordisk
Approval Date:	July 26, 2004

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APPLICATION NUMBER:

20-907/S-007

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)	
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-907
NDA 20-908

CBE-30 SUPPLEMENT

APPROVAL LETTER

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your supplemental new drug applications dated February 3, 2004, received February 4, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella® (estradiol/norethindrone acetate) NDA 20-907/S-007 and Vagifem® (estradiol vaginal tablets) NDA 20-908/S011.

This "Changes Being Effected in 30 days" supplemental new drug application provides: support for the

We completed our review of these supplemental new drug applications and they are approved.

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

If you have any questions, call George Lyght, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

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/s/

Moo-Jhong Rhee
7/26/04 05:00:20 PM

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APPLICATION NUMBER:

20-907/S-007

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**
CBE-30

1. **ORGANIZATION**: DRUDP HFD-580
2. **NDA NUMBER:** 20-907/ SCM 007

3. **SUPPLEMENT DATES:**
   Letter Date: 3-Feb-2004
   Stamp Date: 4-Feb-2004
   Due Date: 3-Aug-2004
4. **AMENDMENTS/REPORTS/DATES:**
   None
5. **RECEIVED BY CHEMIST:** Feb 2004

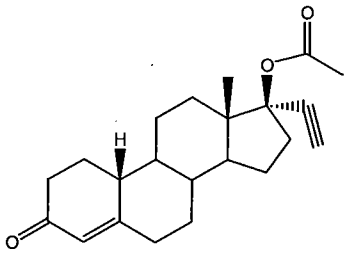
6. **SPONSOR NAME AND ADDRESS**
   Novo Nordisk Pharmaceuticals
   100 College Road West
   Princeton, NJ 08540

7. **DRUG PRODUCT NAME:** Activella

8. **NONPROPRIETARY NAME:** estradiol/norethindrone acetate tablet

9. **DRUG SUBSTANCES NAMES/STRUCTURES**
   Estradiol: Estra-1,3,5(10)-triene-3,17-diol. See USP 24 for the chemical structure.

   Norethindrone acetate (NETA): 17-beta-acetoxy-17-alpha-ethynyl-4-estren-3-one



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

1. **STRENGTH:** 1 mg NETA/ 0.5 mg estradiol

12. **PHARMACOLOGICAL CATEGORY:** estrogen/progestin: for the treatment of VMS

13. **HOW DISPENSED:** Rx

14. **RECORDS AND REPORTS CURRENT:** Yes

15. **RELATED IND/NDA/DMF:**
    DMF [redacted]

16. SUPPLEMENT PROVIDES FOR:

17. COMMENTS:

- The supplement is part of a bundled supplement for NDA 20-907 (Activella), NDA 20-908 (Vagifem), and ANDA 40-312(Innofem).

- DMF [redacted] been reviewed previously and found to be adequate. The most recent review, DMF Review #8 by Dr. B. Cai dated 11-Dec-2002, assessed the stability data from the [redacted] and found the DMF to be adequate.

18. SPECIAL PRODUCTS: No _X

19. CONCLUSIONS AND RECOMMENDATIONS:

The information provided [redacted] is adequate, and the Office of Compliance has recommended approval of the proposed [redacted] Therefore, this CBE-30 supplement may be approved. **Issue an Approval Letter.**

20.	**REVIEWER NAME**	**SIGNATURE**	**DATE COMPLETED**
	J. Salemme, Ph.D. Review Chemist		18-Jun-2004

INIT by MJRhee
Project Mgr: Lyght

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ON ORIGINAL

REVIEW NOTES

Supplement

The sponsor of the NDA has submitted the data from the DMF holder [redacted] to support [redacted]. The same synthesis and controls will be used, and the site has had a satisfactory cGMP inspection for [redacted] in the last two years. The supplement provides release and accelerated stability data for [redacted] at the proposed site, and compares these data to data from [redacted] at the approved site.

A. [redacted]

2. [redacted]

Data to Support the Change to the Proposed Site

Batch Release Data

Lots [redacted] at the current site, and [redacted] at the proposed additional site, have been compared to each other with regard to impurity profile ([redacted]; and total impurities); residual solvents ([redacted]), and by lot-to-lot consistency of values obtained for the tests of the drug substance specification.

Impurity Profile

Data from the [redacted] at the current site are as follows:
Amounts of [redacted] ranged from [redacted], and amounts of [redacted] ranged from [redacted] Total impurities ranged from [redacted]

Data from the [redacted] at the proposed additional site are as follows:
Amounts of [redacted] ranged from [redacted], and amounts of [redacted]. Total impurities ranged from [redacted]

Evaluation: The impurity profiles between the [redacted] at the proposed site and the approved site are comparable.

Redacted 1

Page(s) of trade secret and /or confidential commercial information

[redacted], and the amount of total impurities remained unchanged at approximately

Evaluation: Satisfactory. Batch data are comparable between [redacted], at the current site that at the proposed site. The data demonstrate the [redacted] at the proposed site is comparable to the [redacted] at the current site.

Stability Commitments

Stability commitment for Activella and for Vagifem:
To place on long-term stability the first commercial batch manufactured with the new source of estradiol. The drug product will be tested according to the currently approved specification for each drug product under the approved protocol using ICH guidelines.

Stability commitment for Innofem:
Innofem is not currently marketed in the US. If the drug product is marketed in the future, the sponsor commits to conducting long-term and accelerated stability studies on the first three production batches, conduct routine stability studies on one annual production batch; submit the results in the Annual Report; and update the approved stability protocol to reflect any changes.

Evaluation: The stability commitment for Activella and for Vagifem is acceptable. The stability commitment for Innofem should be assessed by the Chemistry Reviewer in Office of Generic Drugs.

Site Inspection Request
An overall Acceptable recommendation for this [redacted] site was issued by the Office of Compliance on 23-Feb-2004. (See copy of EER report on next page.)

Conclusion:

The batch release and stability data for [redacted] at the additional site demonstrate that the quality of the [redacted] at the new site is comparable to that of the [redacted] at the approved site. Therefore, this CBE-30 supplement is recommended for approval.

APPEARS THIS WAY
ON ORIGINAL

01-JUL-2004 FDA CDER EES Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application	: NDA 20907/007	Sponsor:	NOVO NORDISK
Org Code	: 580		100 COLLEGE RD WEST
Priority	: 4S		PRINCETON, NJ 08540
Stamp Date	: 04-FEB-2004	Brand Name :	ACTIVELLE
PDUFA Date	: 04-AUG-2004	Estab. Name:	
Action Goal	:	Generic Name:	ESTRADIOL; NORETHINDRONATE ACETATE
District Goal	: 30-JUN-2004	Dosage Form:	(AEROSOL)
		Strength :	1 MG/0.5 MG

FDA Contacts:			
G. LYGHT	Project Manager	(HFD-580)	301-827-5424
J. SALEMME	Review Chemist	(HFD-580)	301-827-7330
M. RHEE	Team Leader	(HFD-580)	301-827-4237

Overall Recommendation: ACCEPTABLE on 23-FEB-2004by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile	: CSN	OAI Status:	NONE
Last Milestone	: OC RECOMMENDATION		
Milestone Date	: 23-FEB-04		
Decision	: ACCEPTABLE		
Reason	: BASED ON PROFILE		

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/s/

Jean Salemme
7/12/04 11:45:16 AM
CHEMIST

Moo-Jhong Rhee
7/12/04 12:13:51 PM
CHEMIST
I concur

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-007

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-907 and NDA 20-908

CBE-30 SUPPLEMENT

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

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

Name of Drug Product:	Activella® (estradiol/norethindrone acetate) NDA 20-907/S007 Vagifem® (estradiol vaginal tablets) NDA 20-908/S-011
Date of supplement:	February 3, 2004
Date of receipt:	February 4, 2004

This supplemental application, submitted as "Supplement - Changes Being Effected in 30 days," proposes the following change: [redacted]

This application was filed on April 2, 2004 in accordance with 21 CFR 314.101(a). The application user fee goal date is August 4, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Urologic and Reproductive Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call George Lyght, R.Ph., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Urologic and Reproductive Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
5/18/04 01:13:57 PM
Chief, Project Management Staff

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