

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-001

CHEMISTRY REVIEW(S)

Initial Quality Assessment

OND Division of Metabolism and Endocrinology Products

NDA: 22-001

Applicant: Novo Nordisk Inc.

Stamp Date: 01-MAR-2006

PDUFA Date: 01-JAN-2007

Proposed Proprietary Name: Activella —

Established Name: (estradiol/norethindrone acetate tablets)

Dosage form and strength: tablet of 0.5 mg estradiol/ 0.1 mg norethindrone acetate .

Route of Administration: oral

Indications: Prevention of postmenopausal osteoporosis.

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Chemist Yvonne Yang)

Time goals:

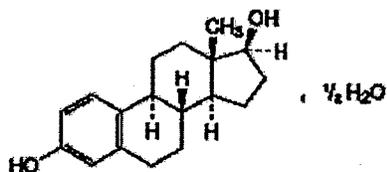
- **Initial Quality Assessment in DFS:** by 01-APR-2006 (NDA assigned to PAL on 11-MAR-2006)
- **Chemistry filing memo in DFS:** by 14-APR-2006
- Filing decision "Day 45": 14-APR-2006 (tentative; to be set by Clinical Division)
- Filing review issues "Day 74": 12-MAY-2006 (tentative; to be set by Clinical Division)
- **Chemistry Review (DR/IR) letter:** by 01-AUG-2006
- Mid-cycle meeting "Month 5": 01-AUG-2006 (tentative; to be set by Clinical Division)
- **Final Chemistry Review "Month 8" in DFS:** by 01-NOV-2006
- PDUFA: 01-JAN-2007

Initial Quality Assessment

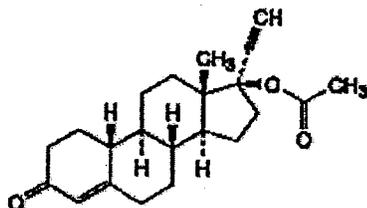
CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
CDRH	<i>Not Applicable</i>
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 27-MAR-2006
DMETS	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>Not Applicable</i>
Pharm/Tox	<i>Not Applicable</i>

Summary:

- This is an electronic NDA, assigned to PAL on 11-MAR-2006. There is a 60-page Quality Overall Summary.
- This NDA is filed as a 505(b)(1) application. This NDA is concurrently submitted to the Division of Reproductive and Urologic Products (DRUP) as an efficacy supplement S-009 to NDA 20-907. The CMC review of this NDA 22-001 will be the lead review for the efficacy supplement to NDA 20-907. Therefore, all administrative procedures (including status and labeling meetings) will be handled through DMEP.
- This NDA is a lower dose of the product approved in NDA 20-907 in DRUP and NDA 21-103 in DMEP, which are twin-NDAs for a higher dose tablet of 1 mg estradiol/ 0.5 mg norethindrone acetate. The applicant is the same for all 3 NDAs.
- Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substances norethindrone acetate (NETA) and estradiol (E2).



Structural Formula of Estradiol Hemihydrate ($C_{18}H_{24}O_2 \cdot \frac{1}{2}H_2O$)



Structural Formula of Norethisterone Acetate ($C_{22}H_{28}O_3$)

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- The drug product is similar to the higher dose product approved in NDA 20-907 (same applicant) with the following differences: amounts of drug substances, _____ hydroxypropylcellulose, amount of film coat, and color of the _____ base of the primary container closure system (a 28-tablet dial-pack consisting of a _____ base and a _____ lid). A composition comparison of the drug product and the approved higher dose is copied below. All excipients are USP/NF-compendial. The manufacturing process of the drug product is similar to that of the approved higher dose product, and the same facilities and equipment are used. The primary container closure system (a 28-tablet dial-pack consisting of a _____ base and a _____ lid) is identical to that used for the approved higher dose product with the exception of the color of the _____ base.
- The drug product is stored at room temperature, protected from light. The following stability data are provided in the NDA for pilot-scale batches PBBA053, PBBA054, and PBBA055, packaged in the to-be-marketed dial pack with the outer cardboard box: 12-month data at 25 °C/60% RH and 30 °C/65% RH, and 6-month at 40 °C/75% RH.

Comparison of the composition of the drug product (0.5 mg estradiol/0.1 mg norethindrone acetate) and the approved higher dose of NDA 20-907 (same applicant):

Table 5 Comparison of Formulations of E2 0.5 mg, NETA 0.1 mg tablet and the E2 1 mg, NETA 0.5 mg tablet

Name of ingredient	Function	Quantity (mg/tablet)	
		E2 0.5 mg, NETA 0.1 mg tablet	E2 1 mg, NETA 0.5 mg tablet
Active ingredients			
_____	_____	—	—

Estradiol _____		0.500	1.00
Norethisterone Acetate _____		0.100	0.500
Other ingredients			
Lactose monohydrate _____			
_____ starch			
Hydroxypropylcellulose _____	_____	—	—

Talc _____			
Magnesium stearate _____			
Theoretical amount			
Hypromellose _____	_____	—	—
Triacetin _____			

Initial Quality Assessment

Critical Issues:

Note: Because this NDA references the approved drug substance section in NDA 20-907 (approved higher dose product) and the manufacture of the drug product is similar to that of the approved higher dose product (with same facilities and equipment), there are very few critical issues found for this NDA.

- Has all information requested during the IND phases, and at the pre-NDA meetings been included?

Note: No chemistry information request was made during the IND phases or at the pre-NDA meeting.

- **Dissolution of the drug product.**

Note: Compared to the approved higher dose (NDA 20-907), the lower dose subject of this review has the _____ r hydroxypropylcellulose _____. Therefore, the dissolution profiles of the 2 products are certain to be different, and the acceptance criteria and test method will require an assessment for this lower dose. _____

- **Limits on degradants in the drug product.**

Note: Compared to the approved shelf life limits on related substances/degradants in the higher dose (NDA 20-907), the proposed shelf life limits on the same related substances/degradants in the lower dose are the same or lower in milligrams per tablet (although the percentage may be higher). Administration of either product is the same, one tablet daily. Therefore, an assessment of the limits on related substances/degradants may not be necessary.

- **Stability of the drug product.**

Note: The drug product is light-sensitive. Although the primary container closure system (a 28-tablet dial-pack consisting of a _____ base and a _____ lid) is identical to that of the approved higher dose product with the exception of the color of the _____ base, the formulation differs for the 2 products. Therefore, the adequacy of packaging in protecting the product from light will be assessed by the reviewer. It should be noted that the primary stability studies were conducted with product packaged in the to-be-marketed dial pack and with the outer cardboard box. The lid of the dial pack is transparent and does not provide much light protection. The adequacy of labeling (i.e., clear instructions on protecting the product from light) will be assessed by the reviewer.

- **Expiration dating period of the drug product.**

Note: The following stability data are provided in the NDA for pilot-scale batches PBBA053, PBBA054, and PBBA055: 12-month data at 25 °C/60% RH and 30 °C/65% RH, and 6-month at 40 °C/75% RH. ICH Q1E guidelines may be used in determining in determining the expiry of the product.

APPEARS THIS WAY ON ORIGINAL

Initial Quality Assessment

Supporting NDA or IND:
NDA 20-907

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
—	II	—	Norethindrone acetate	LOA is provided. <u>No chemistry review is needed:</u> Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance norethindrone acetate.
—	II	—	Norethindrone acetate	LOA is provided. <u>No chemistry review is needed:</u> Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance norethindrone acetate.
—	II	—	Estradiol	LOA is provided. <u>No chemistry review is needed:</u> Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance estradiol.
—	II	—	Estradiol	LOA is provided. <u>No chemistry review is needed:</u> Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance estradiol.
—	III	—	—	LOA is provided. <u>No chemistry review is needed:</u> The referenced item complies with U.S. regulations 21 CFR 177.1350, 177.1520, 178.2010, and 178.3297.
—	III	—	—	LOA is provided. <u>No chemistry review is needed:</u> The referenced item complies with U.S. regulations 21 CFR 177.1640. In addition, this is the same component approved for the product in the referenced NDA 20-907 (same applicant).

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Manufacturers:

DRUG SUBSTANCE	DRUG PRODUCT
<p>Reference is made to approved NDA 20-907 (same applicant) for manufacturing sites. The following is listed in EER for NDA 20-907: CFN CFN CFN CFN</p> <p>Tester: Novo Nordisk A/S Novo Nordisk Park DK-2760 Malov</p> <p>Tester: Novo Nordisk A/S Novo Alle DK-2880 Bagsvaerd</p> <p>Tester: Novo Nordisk A/S Sydmarken 5 DK-2860 Soborg</p>	<p>Manufacturer and tester: Novo Nordisk A/S Novo Nordisk Park DK-2760 Malov</p>

Initial Quality Assessment

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		All facilities are listed.
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		Reference is made to approved NDA 20-907
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		No information was requested.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		In drug product QOS. Clinical batch: PBBA044.
14	Is there a Methods Validation package?	X		Included in Module 3.
15	Is a separate microbiological section included?	X		

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suong Tran
3/27/2006 10:15:36 AM
CHEMIST

paper sign-off 3/27/06

Blair Fraser
3/27/2006 10:21:00 AM
CHEMIST



NDA 22-001

**Activella®
(estradiol/norethindrone acetate) tablets
0.5 mg/0.1 mg**

Novo Nordisk Pharmaceuticals, Inc.

Yvonne Yang, Ph.D.

**Division of Metabolic and Endocrine Products
HFD-510**



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Chemistry Review Data Sheet

1. NDA #: 22-001
2. REVIEW #: #2
3. REVIEW DATE: October-30-2006
4. REVIEWER: Yvonne Yang, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

CMC Review #1

Document Date

Sept-13-2006 (DFS)

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>	<u>Content</u>
Original (EDR)	Feb-28-2006	• Original submission
Amendment	Sept-26-2006	• Updated stability data
		• Revised labeling
Amendment	Oct-06-2006	• Response to IR letter dated Sept-21-2006 to provide for the calculations for environmental assessment

7. NAME & ADDRESS OF APPLICANT:

Name: Novo Nordisk Pharmaceuticals, Inc.
Address: 100 College Road West
 Princeton, NJ 08540
Representative: Rima B. Nassar, Ph.D.
Telephone: (609) 987-5852

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Activella®
- b) Non-Proprietary Name (USAN): Estradiol/norethindrone acetate (E2/NETA)
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 6
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: HRT/Osteoporosis
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: Estradiol/norethindrone acetate (E2/NETA)
E2 0.5 mg/NETA 0.1 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: X Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

	Estradiol	Norethindrone Acetate
Chemical Formula	$C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$	$C_{22}H_{28}O_3$
Chemical Structure		
Chemical Name	Estra-1,3,5(10)-triene-3,17β-diol hemihydrate	3-Oxo-19-nor-17α-pregn-4-en-20-yn-17-yl-acetate
Molecular Mass	281.4	340.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II	—	Norethindrone acetate	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance norethindrone acetate.
—	II	—	Norethindrone acetate	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance norethindrone acetate.
—	II	—	Estradiol	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance estradiol.
—	II	—	Estradiol	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance estradiol.
—	III	—	—	3	Adequate		No chemistry review is needed: The referenced item complies with U.S. regulations 21 CFR 177.1350, 177.1520, 178.2010, and 178.3297.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

III		3	Adequate	No chemistry review is needed: The referenced item complies with U.S. regulations 21 CFR 177.1640. In addition, this is the same component approved for the product in the referenced NDA 20-907 (same applicant).
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-907	Activella® (E2 1.0 mg/NETA 0.5 mg tablets)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending OC		Yvonne Yang
Office of Clinical Pharmacology	Acceptable	DFS Oct-24-2006	Sandra Suarez (HFD-580)
Office of Clinical Pharmacology	Pending		S. W. Johnny Lau (HFD-510)
DMETS	Pending DMETS		
Methods Validation	Acceptable	Oct-30-2006	Yvonne Yang
Environmental Assessment	Acceptable	Oct-30-2006	Yvonne Yang
Microbiology	N/A		

The Chemistry Review for NDA 22-001

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-001 is recommended for **Approval** from the standpoint of chemistry, manufacturing and control **pending (1) an overall acceptable cGMP recommendation from the Office of Compliance, and (2) final labeling.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

The drug product, Activella® (estradiol/norethindrone acetate) tablets, is an immediate release, white, film-coated tablet for oral administration. Each tablet contains 0.5 mg of anhydrous estradiol (E2) and 0.1 mg of norethindrone acetate (NETA). The proposed drug product Activella® is a lower strength dosage form of the currently marketed Activella®, and is intended to be used for once daily oral administration to postmenopausal women with an intact uterus for the treatment of moderate to severe vasomotor symptoms and the prevention of postmenopausal osteoporosis. The formulation for Activella® (E2 0.5 mg/NETA 0.1 mg tablets) is similar to that of the currently marketed Activella® (E2 1.0 mg/NETA 0.5 mg tablets), from the same applicant, except for the content of the two active ingredients, the type of  and the amount of film-coating. The to-be-marketed drug product is supplied as E2 0.5 mg/NETA 0.1 mg strength tablets packaged in a Calendar-Dial-Pack. Each Calendar-Dial-Pack is supplied with 28 tablets designed to dispense one tablet at a time for a 28-day supply. The same packaging materials are used for the proposed lower-dose Activella® and for the marketed Activella® except for the color of the base for the Calendar-Dial-Pack. The manufacturing process for the proposed lower-dose Activella® is similar to that used for the currently marketed Activella® using the same facility, manufacturing equipment, and operating principles.

The proposed storage condition for the drug product is at 25 °C (77 °F) with excursions permitted to 15°-30°C (59°-86°F); the proposed expiry date is 30

Chemistry Assessment Section

months when the tablets are packaged in the Calendar-Dial-Pack stored inside the outer carton.

Drug Substance

Activella® contains two active pharmaceutical ingredients estradiol (E2) and norethindrone acetate (NETA). E2 and NETA are synthetic steroid hormones possessing estrogenic and progestational properties, respectively. The drug substance section of this application is cross referenced to that for the currently marketed product Activella® (NDA 20-907) from the same applicant. Both drug substances are purchased from the same suppliers as those used in the currently marketed product.

Estradiol is a white or almost white, crystalline powder or colorless crystals. —

— E2 used in the formulation meets the requirements of the USP and the Ph. Eur. monograph for E2. Relevant information regarding chemistry, manufacturing, and controls of E2 is provided in DMF — and DMF —, and found adequate to support the original NDA 20-907 (in HFD-580) and the current NDA 22-001 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

Norethindrone acetate is a white or yellowish-white, crystalline powder. —
— NETA used in the formulation meets the requirements of the USP and the Ph. Eur. monograph for NETA. Relevant information regarding chemistry, manufacturing, and controls of NETA is provided in DMF — and DMF — and found adequate to support the original NDA 20-907 (in HFD-580) and the current NDA 22-001 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

— E2 and NETA are used in the proposed formulation, and an acceptance test for particle size distribution is added in addition to the respective tests described in USP/Ph. Eur. to ensure a homogeneous distribution and consistency of dissolution rate of the active ingredients in the tablets.

B. Description of How the Drug Product is Intended to be Used

The proposed Activella® (E2 0.5 mg/NETA 0.1 mg tablets) is a lower strength dosage form of the currently marketed Activella®, and is intended to be used for once daily oral administration to postmenopausal women with an intact uterus for the treatment of moderate to severe vasomotor symptoms and the prevention of postmenopausal osteoporosis. Activella® (E2 0.5 mg/NETA 0.1 mg tablets) is supplied with 28 tablets packaged in a Calendar-Dial-Pack. The Calendar-Dial-Pack is designed to dispense one tablet at a time for a 28-day supply.

Chemistry Assessment Section

The proposed lower strength Activella® (E2 0.5 mg/NETA 0.1 mg tablets) is submitted to the Division of Metabolic and Endocrine Products (HFD-510) as a full NDA for the new indication of prevention of postmenopausal osteoporosis. The same application is submitted to the Division of Reproductive and Urologic Products (HFD-580) as an efficacy supplement, a lower strength for the marketed Activella® (E2 1.0 mg/NETA 0.5 mg tablets, NDA 20-907) for the currently approved indication.

Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3 to 6 month intervals) to determine if treatment is still necessary. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. Patients should be started at the lowest dose.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-001 is recommended for **Approval** from the standpoint of chemistry, manufacturing and control pending the following:

- An overall acceptable cGMP recommendation from the Office of Compliance
- Final labeling

CMC information provided to support the application includes the following:

- CMC information for the drug substance E2 and NETA cross-referenced to the currently marketed Activella® (NDA 20-907, same applicant)
- Adequate CMC information for the lower-strength Activella®
- Acceptable regulatory specification for the lower-strength Activella®
- Sufficient stability data to support the proposed expiration dating period for the lower-strength Activella®

III. Administrative:

- A. Reviewer's Signature in DFS
- B. Endorsement Block: in DFS
- C. CC Block: in DFS

10 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Chemistry- 1

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Yvonne Yang
11/1/2006 07:49:32 AM
CHEMIST

Blair Fraser
11/1/2006 11:45:02 AM
CHEMIST



NDA 22-001

Activella® —
(estradiol 0.5 mg/norethindrone acetate 0.1 mg tablets)

Novo Nordisk Pharmaceuticals, Inc.

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Products
HFD-510



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Chemistry Review Data Sheet

1. NDA #: 22-001
2. REVIEW #: #1
3. REVIEW DATE: August-21-2006
4. REVIEWER: Yvonne Yang, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original (EDR)

Document Date
Feb-28-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Novo Nordisk Pharmaceuticals, Inc.
Address: 100 College Road West
Princeton, NJ 08540
Representative: Rima B. Nassar, Ph.D.
Telephone: (609) 987-5852

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Activella®
b) Non-Proprietary Name (USAN): Estradiol/norethindrone acetate (E2/NETA)
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
 • Chem. Type: 6
 • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: HRT/Osteoporosis



CHEMISTRY REVIEW



Chemistry Review Data Sheet

11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: Estradiol/norethindrone acetate (E2/NETA)
E2 0.5 mg/NETA 0.1 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

	Estradiol	Norethindrone Acetate
Chemical Formula	$C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$	$C_{22}H_{28}O_3$
Chemical Structure		
Chemical Name	Estra-1,3,5(10)-triene-3,17β-diol hemihydrate	3-Oxo-19-nor-17α-pregn-4-en-20-yn-17-yl-acetate
Molecular Mass	281.4	340.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	II	—	Norethindrone acetate	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance norethindrone acetate.
—	II	—	Norethindrone acetate	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance norethindrone acetate.
—	II	—	Estradiol	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance estradiol.
—	II	—	Estradiol	3	Adequate		No chemistry review is needed: Reference is made to the approved NDA 20-907 (same applicant) for all chemistry information on the drug substance estradiol.
—	III	—	—	3	Adequate		No chemistry review is needed: The referenced item complies with U.S. regulations 21 CFR 177.1350, 177.1520, 178.2010, and 178.3297.
—	III	—	—	3	Adequate		No chemistry review is needed: The referenced item complies with U.S. regulations 21 CFR 177.1640. In addition, this is the same component approved for the product in the referenced NDA 20-907 (same applicant).



Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-907	Activella® (E2 1.0 mg/NETA 0.5 mg tablets)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending OC		Yvonne Yang
Biopharm	Pending		Sandra Suarez (HFD-580) S. W. Johnny Lau (HFD-510)
DMETS	Pending DMETS		
Methods Validation	Acceptable		Yvonne Yang
Environmental Assessment	Pending Information to be requested		Yvonne Yang
Microbiology	N/A		

The Chemistry Review for NDA 22-001

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-001 is recommended for **Approval** from the standpoint of chemistry, manufacturing and control **pending (1) a satisfactory response to the information request to be forwarded to the sponsor, (2) an overall acceptable cGMP recommendation from the Office of Compliance, and (3) final labeling including Tradename.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

The drug product, Activella® (estradiol 0.5 mg/norethindrone acetate 0.1 mg tablets), is an immediate release, white, film-coated tablet for oral administration. Each tablet contains 0.5 mg of estradiol (E2) and 0.1 mg of norethindrone acetate (NETA). The proposed drug product Activella® is a lower strength dosage form of the currently marketed Activella®, and is intended to be used for once daily oral administration to postmenopausal women with an intact uterus for the treatment of moderate to severe vasomotor symptoms and the prevention of postmenopausal osteoporosis. The formulation for Activella® (E2 0.5 mg/NETA 0.1 mg tablets) is similar to that of the currently marketed Activella® (E2 1.0 mg/NETA 0.5 mg tablets), from the same applicant, except for the content of two active ingredients, the type of film-coating, and the amount of film-coating. The to-be-marketed drug product is supplied as E2 0.5 mg/NETA 0.1 mg strength tablets packaged in a Calendar-Dial-Pack. Each Calendar-Dial-Pack is supplied with 28 tablets designed to dispense one tablet at a time for a 28-day supply. The same packaging materials are used for the proposed Activella® and for the marketed Activella® except for the color of the base for the Calendar-Dial-Pack. The manufacturing process for the proposed drug product Activella® is similar to that used for the currently marketed Activella® using the same facility, manufacturing equipment, and operating principles.



Chemistry Assessment Section

The proposed storage condition for the drug product is at 25 °C (77 °F) with excursions permitted to 15°-30°C (59°-86°F); the proposed expiry date is _____ months when the tablets are packaged in the Calendar-Dial-Pack stored inside the outer carton.

Drug Substance

Activella® — contains two active pharmaceutical ingredients estradiol (E2) and norethindrone acetate (NETA). E2 and NETA are synthetic steroid hormones possessing estrogenic and progestational properties, respectively. The drug substance section of this application is cross referenced to that for the currently marketed product Activella® (NDA 20-907) from the same applicant. Both drug substances are purchased from the same suppliers as those used in the currently marketed product.

Estradiol is a white or almost white, crystalline powder or colorless crystals. _____

_____ E2 used in the formulation meets the requirements of the USP and the Ph. Eur. monograph for E2. Relevant information regarding chemistry, manufacturing, and controls of E2 is provided in DMF _____ and DMF _____, and found adequate to support the original NDA 20-907 (in HFD-580) and the current NDA 22-001 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

Norethindrone acetate is a white or yellowish-white, crystalline powder. _____

_____ NETA used in the formulation meets the requirements of the USP and the Ph. Eur. monograph for NETA. Relevant information regarding chemistry, manufacturing, and controls of NETA is provided in DMF _____ and DMF _____ and found adequate to support the original NDA 20-907 (in HFD-580) and the current NDA 22-001 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

_____ E2 and NETA are used in the proposed formulation, and an acceptance test for particle size distribution is added in addition to the respective tests described in USP/Ph. Eur. to ensure a homogeneous distribution and consistency of dissolution rate of the active ingredients in the tablets.

B. Description of How the Drug Product is Intended to be Used

Activella® — (E2 0.5 mg/NETA 0.1 mg tablets) is a lower strength dosage form of the currently marketed Activella®, and is intended to be used for once daily oral administration to postmenopausal women with an intact uterus for the treatment of moderate to severe vasomotor symptoms and the prevention of postmenopausal osteoporosis. Activella® — is supplied with 28 tablets



Chemistry Assessment Section

packaged in a Calendar-Dial-Pack. The Calendar-Dial-Pack is designed to dispense one tablet at a time for a 28-day supply.

The proposed lower strength Activella® — (E2-0.5 mg/NETA 0.1 mg tablets) is submitted to the Division of Metabolic and Endocrine Products (HFD-510) as a full NDA for the new indication of prevention of postmenopausal osteoporosis. The same application is submitted to the Division of Reproductive and Urologic Products (HFD-580) as an efficacy supplement, a lower strength for the marketed Activella® (E2 1.0 mg/NETA 0.5 mg tablets, NDA 20-907) for the currently approved indication.

Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3 to 6 month intervals) to determine if treatment is still necessary. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. Patients should be started at the lowest dose.

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-001 is recommended for Approval from the standpoint of chemistry, manufacturing and control pending the following:

- A satisfactory response to the information request to be forwarded to the sponsor (p. 49 of this review)
- An overall acceptable cGMP recommendation from the Office of Compliance
- Final labeling including Tradename.

CMC information provided to support the application includes the following:

- CMC information for the drug substance E2 and NETA cross-referenced to the currently marketed Activella® (NDA 20-907, same applicant)
- Adequate CMC information for the drug product Activella® —
- Acceptable regulatory specification for the drug product Activella® —
- Sufficient stability data to support the proposed expiration dating period for Activella® —

III. Administrative:

- A. Reviewer's Signature in DFS
- B. Endorsement Block: in DFS
- C. CC Block: in DFS

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Draft Labeling

Deliberative Process

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/s/

Yvonne Yang
9/12/2006 03:23:33 PM
CHEMIST

Blair Fraser
9/13/2006 10:19:46 AM
CHEMIST

Activella®
(estradiol /norethindrone acetate) tablets
0.5 mg/0.1 mg
NDA 22-001

**Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls**

Attention: This review is the lead CMC review for NDA 20-907 SE2-009.

Applicant: Novo Nordisk Pharmaceuticals, Inc.
100 College Road West
Princeton, NJ 08540

Indication: Treatment of moderate to severe vasomotor symptoms and the prevention of postmenopausal osteoporosis.

Presentation: The combination drug product is supplied as estradiol 0.5 mg/norethindrone acetate 0.1 mg strength, white, film-coated biconvex tablets and packaged, 28 count, in a Calendar-Dial-Pack, designed to dispense one tablet at a time for a 28-day supply.

EER Status: Pending

Consults:	Clinical Pharmacology:	Acceptable (HFD-580) 24-OCT-2006
	DMETS	Pending
	EA	Categorical exclusion granted under
		21 CFR §25.31(a) for both drugs 30-OCT-2006
	Methods Validation	Acceptable 30-OCT-2006

Original Submission: 28-FEB-2006

Post-Approval Agreements:

None

Drug Substances:

Activella® {estradiol 0.5 mg/norethindrone acetate 0.1 mg} tablets contains two active pharmaceutical ingredients estradiol and norethindrone acetate. The drug substance section of this application cross references that for the currently marketed higher strength product Activella® {estradiol 1.0 mg/norethindrone acetate 0.5 mg} tablets (NDA 20-907) from the same applicant. Both drug substances are purchased from the same suppliers as those used in the currently marketed product.

Estradiol is a synthetic steroid hormone possessing estrogenic properties. Its chemical name is *estra-1,3,5(10)-triene-3,17 β -diol hemihydrate*. It is characterized as a white or almost white, crystalline powder or colorless crystal, a molecular weight of 281.4 Da, and a molecular formula of $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$. It is practically insoluble in water; soluble in acetone, sparingly soluble in alcohol, slightly soluble in ether and in methylene chloride.

Estradiol used in the drug product meets the requirements of the USP and the Ph. Eur. Monographs. Relevant information regarding chemistry, manufacturing, and controls of estradiol is provided in DMF _____ and DMF _____, and was found adequate to support the original NDA 20-907 (in HFD-580) and the current NDA 22-001 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

Norethindrone acetate is a synthetic steroid hormone possessing progestational properties. Its chemical name is *3-oxo-19-nor-17 α -pregn-4-en-20-yn-17-yl-acetate*. It is characterized as a white or yellowish-white, crystalline powder, a molecular weight of 340.5 Da, and a molecular formula of $C_{22}H_{29}O_2$. It is practically insoluble in water, soluble in alcohol and in ether.

Norethindrone acetate used in the drug product meets the requirements of the USP and the Ph. Eur. Monographs. Relevant information regarding chemistry, manufacturing, and controls of norethindrone acetate is provided in DMF _____ and DMF _____, and was found adequate to support the original NDA 20-907 (in HFD-580) and the current NDA 22-001 (in HFD-510). Stability data to support the re-test period have been provided in the DMF.

To ensure a homogeneous distribution and consistency of dissolution rate of the active ingredients in the drug product, _____ estradiol and norethindrone acetate are used in the proposed drug product formulation. A specification for particle size distribution was added to the list of specifications described in USP/Ph. Eur.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product Activella® {estradiol 0.5 mg/norethindrone acetate 0.1 mg} tablets is a lower strength dosage form of the currently marketed Activella® {estradiol 1.0 mg/norethindrone acetate 0.5 mg} tablets. The drug product is an immediate release, tablet for oral administration.

Each white, film-coated, round (6 mm diameter), biconvex, tablet contains 0.5 mg of estradiol and 0.1 mg of norethindrone acetate. The tablets are embossed with NOVO 291 on one side and Apis on the other side.

The formulation for Activella® {estradiol 0.5 mg/norethindrone acetate 0.1 mg} tablets is similar to that of the currently marketed Activella® tablets, from the same applicant, except for the content of the two active ingredients, the type of _____ and the amount of film-coating. The composition of the tablet is estradiol _____ norethindrone acetate (0.100 mg),

lactose monohydrate (), starch hydroxypropylcellulose
, talc magnesium stearate hypromellose
and triacetin for a total tablet weight of 82 mg.

Specifications for the drug product include: appearance; identification by TLC and HPLC; assay by HPLC; purity, impurities, related substances, and content uniformity by HPLC; loss on drying; and dissolution. All test methods have been appropriately validated for their intended purpose.

The to-be-marketed drug product is supplied as tablets packaged in a Calendar-Dial-Pack. Each Calendar-Dial-Pack is supplied with 28 tablets designed to dispense one tablet at a time for a 28-day supply. Except for the color of the base for the Calendar-Dial-Pack, the same packaging materials proposed for the lower strength Activella® are currently used for the marketed Activella®.

Submitted real-time stability data for 18 months and accelerated stability data support the proposed expiration dating of 30 months for drug product are packaged in the Calendar-Dial-Pack stored inside the outer carton at 25 °C (77 °F) with excursions permitted to 15°-30°C (59°-86°F). Do not refrigerate.

Conclusion: Drug product is satisfactory.

Additional Items:

The applicant has adequately responded to all deficiencies noted in the 21-SEP-2006 information request letter.

All associated Drug Master Files (DMFs) are adequate or the pertinent information has been adequately provided in the application.

Overall Conclusion:

From a CMC perspective, the application is recommended for **approval** pending an overall acceptable cGMP recommendation and final labeling.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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this page is the manifestation of the electronic signature.**

/s/

Blair Fraser
11/14/2006 12:37:36 PM
CHEMIST

MEMORANDUM

Date: December 15, 2006

To: NDA 22-001

From: Yvonne Yang, Ph.D.
Chemist Reviewer

Subject: Overall Compliance Recommendation

An overall acceptable cGMP status has been granted by the Office of Compliance on December-15-2006 (see attached EER report for details).

NDA 22-001 is recommended for **Approval** from the standpoint of chemistry, manufacturing and control.

Cc: NDA 22-001
DMEP/Division file/P Madara
DRUP/Division file/A Suliman
ONDQA/Y Yang/S Tran/B Fraser

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 22001/000 Action Goal:
Stamp: 01-MAR-2006 District Goal: 02-NOV-2006
Regulatory Due: 01-JAN-2007 Brand Name: ACTIVELLA
Applicant: NOVO NORDISK INC Estab. Name:
LD(ESTRADIOL/NORETHINDRO
NO CITY, , XX Generic Name: ESTRADIOL /
6S NORETHINDROME
ACETATE
Priority: 510 Dosage Form: (TABLET)
Org Code: Strength: 0.5 MG / 0.1 MG

Application Comment: CMC OF THIS NDA 22001 IS IDENTICAL TO CMC OF SUPPLEMENTAL
NDA 20907/SE2-009. DRUG SUBSTANCE SECTION OF NDA 22001
REFERENCES APPROVED DRUG SUBSTANCE SECTION IN NDA 20907 (SAME
APPLICANT). (on 23-MAR-2006 by S. TRAN O 301-796-1764)

FDA Contacts: P. MADARA 301-796-1249 , Project
Manager
Chiefst Y. YANG 301-796-1777 , Review
Leader S. TRAN 301-796-1764 , Team

Overall Recommendation: ACCEPTABLE on 15-DEC-2006 by S. ADAMS
(HFD-322) 301-827-3031

Establishment: CFN [REDACTED] FE1 [REDACTED]

DMF No: [REDACTED] AADA:
Responsibilities: [REDACTED]

Profile: CSN OAI Status: NONE

EMilestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO OC TRANS	27-MAR-2006			
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SUBMITTED TO DO ADANSS	27-MAR-2006	GMP		
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ASSIGNED INSPECTION T ADANSS	03-APR-2006	GMP		
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INSPECTION SCHEDULED ADANSS	24-MAY-2006		28-JUN-2006	
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INSPECTION PERFORMED ADANSS	26-JUN-2006		26-JUN-2006	
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INSPECTION PERFORMED TARA.GOOEN	28-JUN-2006		28-JUN-2006	
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Complete Summary of Findings:

[REDACTED]

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Deliberative Process

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QC RECOMMENDATION 12-JUL-2006 INSPECTION
ADAMSS ACCEPTABLE
DISTRICT RECOMMENDATION

Establishment: CFN 9613234 FEI 3002807732
NOVO NORDISK
SYDMARKEN 5
SOEBERG, DA DK 2860

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CTL QAI Status: NONE
0 15-DEC-2006 FDA CDER EES Page
4 of 6

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Event Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO QC TRANS	27-MAR-2006			
SUBMITTED TO DO ADAMSS	27-MAR-2006	GMP		
ASSIGNED INSPECTION T ADAMSS	03-APR-2006	GMP		
INSPECTION SCHEDULED IRIVERA	06-NOV-2006		01-DEC-2006	

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INSPECTION PERFORMED 30-NOV-2006 Report.txt
ADAMSS 30-NOV-2006
DO RECOMMENDATION 01-DEC-2006 ACCEPTABLE
ADAMSS INSPECTION
NO 483 ISSUED. BASED ON INVESTIGATOR'S RECOMMENDATION. AWAITING EIR.
QC RECOMMENDATION 01-DEC-2006 ACCEPTABLE
ADAMSS DISTRICT RECOMMENDATION

Establishment: CFN 9613235 FEI 3003037054
NOVO NORDISK
NOVO NORDISK PARK
MAALEOV, DA DK-2760

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TCM QAI Status: NONE

Event Name Creator	Date	Type	Insp. Date	Decision & Reason
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SUBMITTED TO QC TRANS	27-MAR-2006			
SUBMITTED TO DO ADAMSS	27-MAR-2006	GMP		
ASSIGNED INSPECTION T ADAMSS	03-APR-2006	GMP		
INSPECTION SCHEDULED IRIVERA	06-NOV-2006		08-DEC-2006	
INSPECTION PERFORMED ADAMSS	07-DEC-2006		07-DEC-2006	

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Report.txt
 DO RECOMMENDATION 15-DEC-2006 ACCEPTABLE
 ADAMS
 INSPECTION
 NO 483 ISSUED. BASED INVESTIGATOR'S RECOMMENDATION. AWAITING EIR.
 OC RECOMMENDATION 15-DEC-2006 ACCEPTABLE
 ADAMS
 DISTRICT RECOMMENDATION

Establishment: CFN 9616213 FEI
 MONO HORDISK A/S
 KROGSHOLVED 49
 BAGSVAERD, DA

DHF No: AADA:
 Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CTL OAI Status: NONE

EMilestone Name Creator	Date	Type	Insp. Date	Decision & Reason
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ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT

SUBMITTED TO OC 27-MAR-2006 Page 9

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 TRANS
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 INSPECTION PERFORMED 03-APR-2006
 FACTS_EES

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

INSPECTION PERFORMED 28-NOV-2006 28-NOV-2006
 ADAMS

INSPECTION SCHEDULED 01-DEC-2006 28-NOV-2006
 ADAMS

DO RECOMMENDATION 01-DEC-2006 ACCEPTABLE
 ADAMS

INSPECTION

BASED ON INVESTIGATOR'S RECOMMENDATION NO 483 ISSUED. AWAITING EIR.

OC RECOMMENDATION 01-DEC-2006 ACCEPTABLE
 ADAMS

DISTRICT RECOMMENDATION

Establishment: CFN FEI

DHF No: 2033 AADA:
 Responsibilities:

Profile: CSN OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason
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/s/

Yvonne Yang
12/15/2006 03:03:23 PM
CHEMIST

Blair Fraser
12/15/2006 03:44:53 PM
CHEMIST