

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-103**

**Chemistry Review(s)**

**DIVISION OF Metabolism and Endocrine DRUG PRODUCTS**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA#: 21-103**

**CHEM.REVIEW #: 2**

**REVIEW DATE: 4-10-00**

**SUBMISSION TYPE**  
AMENDMENT

**DOCUMENT DATE**  
4-10-00

**CDER DATE**  
4-10-00

**ASSIGNED DATE**  
4-10-00

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME**

Proprietary: Activella (Previously Activelle)  
Nonproprietary/USAN: Estradiol/Norethindrone  
Chem. Type/Ther. Class: 6S

**PHARMACOL. CATEGORY/INDICATION:**

Prevention of osteoporosis.

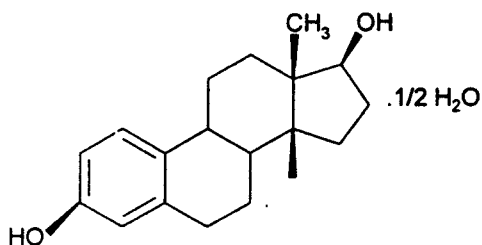
**DOSAGE FORM:** Tablet

**STRENGTHS:** 1 mg Estradiol/ 0.5 mg Norethindrone Acetate

**ROUTE OF ADMINISTRATION:** Oral

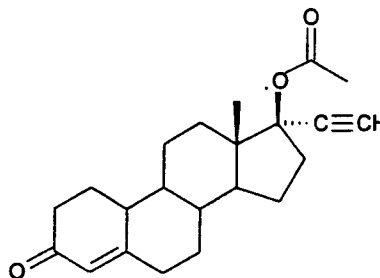
**DISPENSED:**  Rx  OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**



Estradiol, USP  
Estradiol hemihydrate, Ph.Eur

C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>. 1/2 H<sub>2</sub>O  
Molecular Weight: 281.4  
CAS # 50-28-2



Norethindrone acetate, USP  
Norethindrone acetate, Ph.Eur

C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>  
340.5  
51-98-9

**SUPPORTING DOCUMENTS:** See Review #1 of NDA 21-103

**RELATED DOCUMENTS:**

Reviews #1 & #2 of NDA 20-907  
Review of Sup. SCM-001 of NDA 20-907  
Review of Sup. SLR-002 of NDA 20-907

**CONSULTS:** None

**REMARKS/COMMENTS:**

Chemistry Review #1 for this NDA indicated that the application was approvable from a Chemistry point of view, pending satisfactory labeling in the "Description" and "How Supplied" sections of the Package insert. The amendment, dated 4-10-00 provides up-dated and satisfactory labeling for these sections of the Package insert. Accordingly, the application is now approvable from a Chemistry point of view.

**CONCLUSION & RECOMMENDATIONS:**

Satisfactory CMC information has been provided, and the application is approvable from a Chemistry point of view,

cc:  
Orig. NDA 21-103  
HFD-510/Division File  
HFD-580/ Division File  
HFD-510/Sheldon Markofsky  
HFD-510/R. Hedin CSO)  
HFD-510/D-G. Wu (Team Leader)

*SM*  
\_\_\_\_\_  
Sheldon Markofsky, Review Chemist

*4-10-00*

R/D Init by: Team Leader

filename: n21103-Rev2

*4/10/00*

**DIVISION OF Metabolism and Endocrine DRUG PRODUCTS**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA#: 21-103**

**CHEM.REVIEW #: 1**

**REVIEW DATE: 4-6-00**

<b><u>SUBMISSION TYPE</u></b>	<b><u>DOCUMENT DATE</u></b>	<b><u>CDER DATE</u></b>	<b><u>ASSIGNED DATE</u></b>
ORIGINAL	6-10-99	6-11-99	6-21-99
AMENDMENT	8-17-99	8-18-99	8-20-99
CORRESPONDANCE	3-7-00	3-8-00	3-14-00
AMENDMENT	4-5-00	4-6-00	4-6-00

**NAME & ADDRESS OF APPLICANT:**

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

**DRUG PRODUCT NAME**

Proprietary: Activella (Previously Activelle)  
Nonproprietary/USAN: Estradiol/Norethindrone  
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**PHARMACOL. CATEGORY/INDICATION:**

Prevention            of osteoporosis.

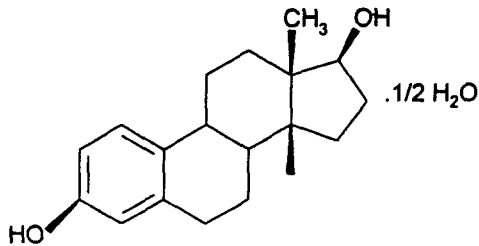
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**STRENGTHS:** 1 mg Estradiol/ 0.5 mg Norethindrone Acetate

**ROUTE OF ADMINISTRATION:** Oral

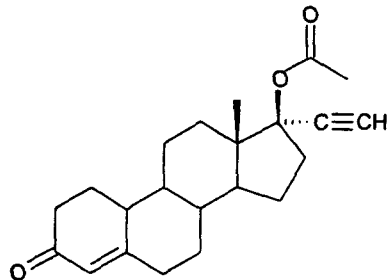
**DISPENSED:**   X   Rx        OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:**



Estradiol, USP  
Estradiol hemihydrate, Ph.Eur

C<sub>18</sub>H<sub>24</sub>O<sub>2</sub> · 1/2 H<sub>2</sub>O  
Molecular Weight: 281.4  
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Norethindrone acetate, USP  
Norethindrone acetate, Ph.Eur

C<sub>22</sub>H<sub>28</sub>O<sub>3</sub>  
340.5  
51-98-9

**SUPPORTING DOCUMENTS:** See Review #1 of NDA 20-907

**RELATED DOCUMENTS:**

Reviews #1 & #2 of NDA 20-907  
Review of Sup. SCM-001 of NDA 20-907  
Review of Sup. SLR-002 of NDA 20-907

**CONSULTS:** None

**REMARKS/COMMENTS:**

This application (NDA 21-103) was submitted as type 6 NDA for Activelle, an approved drug for NDA 20-907. Thus, NDA 21-103 (for the prevention of osteoporosis) and NDA 20-907 (for relief of estrogen deficiency symptoms) are for the same drug product. The chemistry, manufacturing, and controls for this NDA are covered in Reviews # 1 (7-30-98) and # 2 (11-4-98), for NDA 20-907, written by Maria Ysem (HFD-180). Similarly, a CBE supplement to NDA 20-907, dated 7-8-99 (& a corresponding amendment dated 8-17-99) for the relocation of a was reviewed, for this NDA (21-103) as well as for NDA 20-907, by Jila Boal (HFD-580) on 10-21-99. The name change from Activelle to Activella, as communicated to the Division in a correspondence, dated 3-7-00, was approved in the review of NDA 20-907/SLR-002 (reviewed by David Lin, HFD-580, dated 2-1-00). The amendment, dated 4-5-00, provided labeling for the dispenser and carton used in the packaging of Activella tablets.

The above mentioned related reviews deemed their corresponding applications acceptable. Accordingly, from a Chemistry point of view, these reviews satisfactorily support NDA 21-103. The cGMP compliance status for this NDA is acceptable

**CONCLUSION & RECOMMENDATIONS:**

Satisfactory CMC information has been provided, and the application is approvable from a Chemistry point of view, pending satisfactory labeling in the "Description" and "How Supplied" sections of the Package insert.

cc:  
Orig. NDA 21-103  
HFD-510/Division File  
HFD-580/ Division File  
HFD-510/Sheldon Markofsky  
HFD-510/R. Hedin CSO)  
HFD-510/D-G. Wu (Team Leader)

SM - 4-6-00  
Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

SM

filename: n21103a

4/7/00

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pages of trade

secret and/or

confidential

commercial

information