DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 20-908 **Chemistry Review # 2** **Review Date**: 3-25-99 MAR 25 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	3-18-99	3-24-99	3-24-99
Amendment	3-19-99	3-24-99	3-24-99
Facsimile 1	3-24-99	3-24-99	3-24-99
Facsimile 2	3-24-99	3-24-99	3-24-99
Facsimile 3	3-25-99	3-25-99	3-25-99

NAME AND ADDRESS OF APPLICANT
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08541

DRUG PRODUCT NAME
Proprietary: Vagifem
Non-proprietary/USAN: Estradiol vaginal tablet
Compendium: does not apply
Code name/number: None
Chem. Type/Ther. Class: 3 S

ANDA SUITABILITY PETITION/DESI/PATENT STATUS: N/A

PHARMACOL. CATEGORY/INDICATION: Atrophic vaginitis, a component of urogenital syndrone associated with the estrogen deficiency of menopause
DOSAGE FORM: Vaginal tablets
STRENGTHS: 1) 25 mcg estradiol tablets
ROUTE OF ADMINISTRATION: Vaginal

Dispensed: By prescription

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:
Estradiol- Estra-1,3,5(10)-triene-3, 17-diol (17 β); Estra-1,3,5(10)-triene-3, 17 β-diol;

$C_{18}H_{24}O_2$ / 272.39

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS
NDA 20-908, document date 5-29-99, Amendments to NDA 20-908, dated 10-22-98 and 12-10-98
CONSULTS
None

REMARKS/COMMENTS

Several deficiencies were sent to the sponsor on 3-15-99 based on the preliminary review of the NDA. The sponsor responded to those deficiencies via Amendments dated 3-18-99 and 3-19-99. Based on the preliminary review of the amendments the sponsor was asked to revise the release rate specifications. The facsimile 1 and 2 contain various arguments by the sponsor on the justification of the dissolution specification. The facsimile 3 contains the final approved specifications for the drug product.

The inspection report attached in the Chemistry Review #1 suggested that Novo Nordisk A/S, Hillerogade 31, DK 2200, Copenhagen facility has not been inspected. Based on a communication (attached) with the sponsor, the site is a QC site for analysis of inactive raw materials. The FDA compliance coordinator decided since the site is for QC of inactive raw materials, no inspection is needed
The OC recommendation is now acceptable in the EES system.

CONCLUSION AND RECOMMENDATIONS

With respect to CMC the application can be approved.

/S/

Amit K. Mitra, Ph.D

cc: NDA orginal
HFD-580/A. K. Mitra
HFD-580/M. J. Rhee, Ph.D
HFD-580/J. Mercier
HFD-580/Div. File
R/D Init. By

/S/ 5/25/99

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 20-908 **Chemistry Review # 1** **Review Date**: 3-24-99

MAR 24 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	5-29-98	6-1-98	6-9-98
Amendment	10-22-98	10-23-98	10-27-98
Amendment	12-10-98	12-11-98	12-11-98

NAME AND ADDRESS OF APPLICANT
Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08541

DRUG PRODUCT NAME
Proprietary: Vagifem
Non-proprietary/USAN: Estradiol vaginal tablet
Compendium: does not apply
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Chem. Type/Ther. Class: 3 S

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$C_{18}H_{24}O_2$ / 272.39

SUPPORTING DOCUMENTS: IND , DMF
DMF , DMF , DMF DMF
DMF

Type/No.	Subject	Holder	Status	Review Date	Letter Date
	Lackered and printed aluminum foil		Adequate (Reviewed by Dr. A. K. Mitra)	3-1-99	
	Estradiol		Adequate (Reviewed by Dr. D. Lin) in conjunction with NDA 20-847	2-26-98	
	Estradiol		Adequate (Reviewed by Dr.B. Cai) in conjunction with ANDA 40-275	12-15-98	
	(polypropylene resin)		Adequate (See Chemistry Review # 4 by Dr. A. Mitra) to support NDA 20-908	3-1-99	3-5-99
	(PVC for blister pack)		Adequate (See Chemistry Review #1 by Dr. A. Mitra) to support NDA 20-908	3-1-99	3-4-99
	polyethylene resin		Adequate (See Chemistry Review # 3 by Dr. A. Mitra) to support NDA 20-908	3-1-99	3-4-99

The DMF was not reviewed since the CFR references and the qualitative compositions are provided by the sponsor of the NDA.

RELATED DOCUMENTS

None

CONSULTS

1. The proposed trademark "Vagifem" was sent to the labeling and nomenclature committee on 9-30-98. The trademark Vagifem is acceptable.
2. The EER was sent on 9-3-99. The inspection results are satisfactory for all sites except the Copenhagen facility which was not inspected. The next inspection of the facility is scheduled in April-May.

REMARKS/COMMENTS

The application was declared fileable contingent on 12 months stability data including data analysis is available. The amendment dated 12-04-97 contains 12 months room temperature stability data. The amendment dated 10-22-98 incorporated various changes. Those changes include "Multivariate classification of HPMC", Identification of estradiol in tablet, determination of particle size distribution in suspensions using Coulter Counter, Operation of water activity measuring equipment, minor changes in assay content uniformity and identification of estradiol in tablets, specification for purified water to conform to USP, changes related to blister foil, plunger rod (mainly name changes). The changes described in the amendment are discussed in appropriate sections of the review. The changes in the DMF will be reviewed in the individual DMF review.

Based on the preliminary review of the NDA the draft deficiency letter below was sent to the sponsor of the NDA on 3-15-99 in the form of Comments and Information Requests. Since that time the responses from the sponsor regarding those Comments and Requests were received via facsimile, and those are reviewed in Chemistry Review #2.

CONCLUSION AND RECOMMENDATIONS

With regard to chemistry, manufacturing and controls, the application is approvable pending some additional information and changes. See the draft deficiency letter.

DRAFT DEFICIENCY LETTER

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 specifications on release and shelf-life.

Stability of the drug product

1. The specifications for single unknown impurity and sum of impurities (total degradation products) were not provided at shelf life. Specifications for those attributes at shelf life should be provided; otherwise, proper justification should be provided.

2. A shelf life of 3 years can not be supported since the analytical method (for related substances) to arrive at this conclusion was semi-quantitative and dissolution method used is not the current dissolution method. Therefore, a two year shelf-life is granted based on 12 months 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.

The labeling comments were already conveyed to the project manager.

/S/

Amit K. Mitra, Ph.D

cc: NDA orginal
HFD-580/A. K. Mitra
HFD-580/M. J. Rhee, Ph.D
HFD-580/J. Mercier
HFD-580/Div. File
R/D Init. By 3/24/99