

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

CHEMISTRY REVIEW(S)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-582	CHEM. REVIEW #: 3	REVIEW DATE: 8/14/97	
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE:
ORIGINAL	1/11/96	9/16/96	1/31/96
AMENDMENT	3/27/97		
AMENDMENT	5/14/97		
AMENDMENT	6/3/97		
AMENDMENT	7/11/97		
AMENDMENT	7/30/97		

NAME & ADDRESS OF APPLICANT: Organon INC.
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

DRUG PRODUCT NAME

Proprietary: Follistim
Nonproprietary/USAN: Follitropin beta
Common Name: Recombinant Follicle Stimulating Hormone
Code Name/#: Org 32489
Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION:

Hormone, stimulating multiple ovarian follicular growth
To stimulate multiple ovarian follicular growth in pituitary down regulated infertile women undergoing in vitro fertilization and embryo transfer.

DOSAGE FORM: Lyophilized powder for injection
STRENGTHS: 75 IU or 150 IU/ vial
each in 2 mL
ROUTE OF ADMINISTRATION: Subcutaneous or intramuscular
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chem. Rev. #1

REMARKS/COMMENTS:

This NDA, originally submitted on 1/11/96, has been found not satisfactory and a Not Approval Letter dated 4/10/97 was issued to the applicant.

The amendment dated 3/27/97 provides for responses to inquiries made by the reviewer regarding a high level of oxidation products at current storage conditions for a shelf-life of 24 months.

The amendment dated 5/14/97 provides for responses to deficiencies outlined in the Not Approval letter dated 4/10/97.

The amendments dated 6/3/97 provides for a response to our inquiry regarding the decreasing biological activity of the product during storage.

The amendments dated 7/11/97 provides for comments for the statements regarding established name, follitropin alfa and beta to be added in the Description section of the package insert.

The amendment dated 7/30/97 provides for the Phase IV commitments requested in a fax regarding storage conditions, a shorten expiration dating, and other issues related to vial filling by mass.

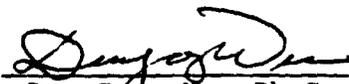
The remaining deficiencies related to the drug substance described in the DMF have been adequately responded (see review # 3 for DMF

The manufacturing facility at previously found unacceptable, is now acceptable

CONCLUSIONS & RECOMMENDATIONS:

From chemistry standpoint, this NDA can now be approved. In the approval letter, the firm should be reminded of the Phase IV commitments made in the amendments dated 5/14/97 and 7/30/97. Also, the following statement regarding the established name, follitropin beta, should be included in the letter:

Orig. NDA 20-582
HFD-580/Division File
HFD-510/D.G. Wu
HFD-580/L. Pauls/M.Rhee


Duu-Gong Wu, Ph.D
Team Leader II, DNDCII
Filename: 20582.ND3

R/D Init by:

MAR 22 1997

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

<u>NDA #:</u> 20-582	<u>CHEM. REVIEW #:</u> 2	<u>REVIEW DATE:</u> 3/22/97
<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>ASSIGNED DATE:</u>
ORIGINAL	1/11/96	1/31/96
AMENDMENT	1/9/97	
AMENDMENT	2/5/97	
AMENDMENT	2/11/97	
AMENDMENT	2/14/97	
AMENDMENT	3/11/97	

NAME & ADDRESS OF APPLICANT: Organon INC.
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052

DRUG PRODUCT NAME
Proprietary: Follistim
Nonproprietary/USAN: Follitropin beta
Common Name: Recombinant Follicle Stimulating Hormone
Code Name/#: Org 32489
Chem. Type/Ther. Class: 3S

PHARMACOL. CATEGORY/INDICATION:

Hormone, stimulating multiple ovarian follicular growth
To stimulate multiple ovarian follicular growth in pituitary down
regulated infertile women undergoing in vitro fertilization and embryo
transfer.

DOSAGE FORM: Lyophilized powder for injection
STRENGTHS: 75 IU or 150 IU/ vial
each in 2 mL
ROUTE OF ADMINISTRATION: Subcutaneous or intramuscular
DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
See Chem. Rev. #1

REMARKS/COMMENTS:

The amendment dated 1/9/97 provides for responses to information requests contained in an FDA letter dated 12/5/96. The information request was based on deficiencies outlined in the draft letter for the chemistry review #1 dated 11/26/96.

The amendment dated 2/11/97 provides for a page that was inadvertently omitted from the 1/7/97 amendment.

The amendments dated 2/5/97 and 2/14/97 provides information concerning the quality of color photocopies of the IEF gels provided in the 1/9/97 amendment.

The amendment dated 3/11/97 provides for the photographs of IEF gels for a total of 10 lots of recFSH drug substance.

An alternate tradename, Puregon, has been found acceptable by the CDER Labeling and Nomenclature Committee because its similarity to other products.

The Microbiology Consult Review # 2 dated 12/20/96 has been completed by Dr. Hussong and the NDA is recommended for approval.

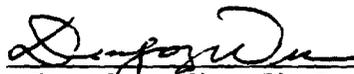
The results for cGMP inspections are still pending.

CONCLUSIONS & RECOMMENDATIONS:

From chemistry standpoint, this NDA is approvable pending:

- (1) a satisfactory response to the deficiencies outlined in the draft letter of this review and those listed the review #2 for DMF which will be forwarded to the DMF holder in a separate letter.
- (2) A satisfactory cGMP inspection for all facilities listed in the NDA and referenced DMF.
- (3) The resolution of issues concerning the established name "follitropin beta".

Orig. NDA 20-582
HFD-580/Division File
HFD-510/D.G. Wu
HFD-580/L. Pauls/M.Rhee



Duu-Gong Wu, Ph.D
Acting Team Leader II, DNDCII
Filename: 20582.ND2

R/D Init by:

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing, and Controls

<u>NDA #:</u>	20-582	<u>CHEM.REVIEW #:</u>	1	<u>REVIEW DATE:</u>	11/26/96
<u>SUBMISSION TYPE</u>		<u>DOCUMENT DATE</u>		<u>CDER DATE</u>	
ORIGINAL		1/11/96		1/16/96	1/31/96
AMENDMENT		5/14/96			
AMENDMENT		5/16/96			
AMENDMENT		10/8/96			
AMENDMENT		10/10/96			

NAME & ADDRESS OF APPLICANT: Organon INc.
 375 Mt. Pleasant Avenue
 West Orange, New Jersey 07052

DRUG PRODUCT NAME

Proprietary: Follistim
Nonproprietary/USAN: Follitropin beta
Common Name: Recombinant Follicle Stimulating Hormone
Code Name/#: Org 32489
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION:

Hormone, stimulating multiple ovarian follicular growth
 To stimulate multiple ovarian follicular growth in pituitary down regulated infertile women undergoing in vitro fertilization and embryo transfer.

DOSAGE FORM: Lyophilized powder for injection
STRENGTHS: 75 IU or 150 IU/ vial
 each in 2 mL
ROUTE OF ADMINISTRATION: Subcutaneous or intramuscular
DISPENSED: X Rx OTC

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

See page 3

REMARKS/COMMENTS:

Follistim drug product for treatment of female infertility is a sterile lyophilized drug product containing either 75IU or 150 IU of FSH, packaged in 2 mL vials to be reconstituted with 1 mL of sodium chloride injection 0.45%.

It is a product of recombinant Human Follicle Stimulating Hormone. Human Follicle Stimulating Hormone, or hFSH, is a glycoprotein composed of two non-covalently-bound alpha and beta subunits at a one to one ratio. The glycoprotein is produced in genetically engineered Chinese Hamster Ovary (CHO) cells carrying DNA sequences coding for the alpha and beta subunits of hFSH. The production CHO cells were generated by transfecting a plasmids containing DNA sequences coded for rhFSH α and β subunit into cells, which was then integrated into and amplified in the host chromosomes. The amino acid sequence of the product is identical to that of human urine-derived FSH.

The amendment dated 5/14/96 provides for response to a comment by the CDER Nomenclature and Labeling Committee regarding the proposed trade name "Follistim".

The amendment dated 5/16/96 provides for changes to update various sections of chemistry, manufacturing, and controls information.

The amendment dated 10/8/96 provides for a new testing facility, to replace a previously listed facility, for in-vivo FSH bioassay.

The amendment dated 10/10/96 provides for an alternate tradename "PREGON" for the drug product.

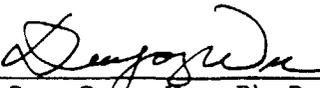
CONCLUSIONS & RECOMMENDATIONS:

From chemistry standpoint, this NDA is not approvable due to inadequate chemistry information submitted in this NDA and the referenced DMF. See draft letter for the deficiencies related to this NDA to be conveyed to the applicant. The deficiencies concerning DMF will be forwarded to the DMF holder in a separate letter (see Chem. Review #1 dated 11/25/96 for DMF). Also, one information request needs to be forwarded to the applicant for the EA review.

Other issues related to chemistry include:

- (1) The acceptance of the alternate tradename "PREGON" and the established name "follitropin beta" are still under consideration by the CDER Labeling and Nomenclature Committee and USAN Council, respectively.
- (2) In a Microbiology Consult Review completed on 9/13/96, Dr. Hussong of HFD 160 indicated that this application is not recommended for approval for reasons of sterility assurance (see attached Consult Review dated 9/13/96).
- (3) The result of cGMP inspection for all facilities listed in the DNA and referenced DMF is still pending.

Orig. NDA 20-582
HFD-580/Division File
HFD-510/D.G. Wu
HFD-580/L. Pauls/M.Rhee



Duu-Gong Wu, Ph.D
Acting Team Leader II, DNDCII
Filename: 20582.ND1

R/D Init by:

Support Documents :

RELATED DOCUMENTS (if applicable):

DMF DMF

CONSULTS:

Microbiology section

- HFD-160 for consults.

PATENT INFORMATION

Patent information is included in Vol. 1.1. The US patent No. 5,270,057 and 4,589,402 own by Akzo (Organon) covered the formulation, composition/or method of use for Follistim. The applicant also indicated that there is no known patent

Debarment Certification

A Debarment Certification dated 1/2/96 as required under the Generic Drug Enforcement Act of 1992 has been included in Vol. 1.1.

Satisfactory.