

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-582

ADMINISTRATIVE DOCUMENTS

Food and Drug Administration
Rockville MD 20857

NDA 20-582

APR 10 1997

Organon, Inc.
Attention: Albert P. Mayo
Director, Regulatory Affairs
375 Mt. Pleasant Ave.
West Orange, NJ 07052

Dear Mr. Mayo:

Please refer to your new drug application dated January 10, 1996, received January 11, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Follistim (follitropin beta), 75 IU and 150 IU vials.

We acknowledge receipt of your submissions dated February 9, May 14 and 16, June 3 and 21, September 27, October 4, 8 and 10, November 19, 20, 22 and 26, 1996; January 9, February 5, 11 and 14, and March 11, 17, and 27 and April 8, 1997. The original User Fee goal date for this application was January 11, 1997. Your submission of January 9, 1997 extended the User Fee goal date to April 10, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Establishment Inspection

During recent inspections of one of the manufacturing facilities for your NDA, specifically a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

The following additional deficiencies, although not reasons for the non-approval of your application, must be addressed in your response:

Manufacturing/Quality Controls

Drug Substance

1. The analytical results for oxidized FSH in 25 batches of the drug substance have not been included in Attachment VF as indicated in Vol. 4.1, page 10, Response 6. This document should be submitted.
2. Data to justify a specification of % for the oxidized form of FSH should be provided. In addition, please clarify whether this limit is based on stability testing of the samples stored at the proposed storage temperature of -20°C.

3. Certificates of analysis for representative lots of drug substance tested according to the revised tests and specifications should be provided.
4. The document provided in Vol. 4.2, Attachment IX, pages 278-280 was not a protocol for qualification of a future reference standard as requested in our letter dated December 5, 1996. Such a protocol should describe a set of tests for extensive characterization of a new reference standard. The protocol needs to be approved so that a change in reference standard can be reported in an annual report. Without this information, a prior approval supplement will be required for the change.

Drug Product

1. Tests and specifications
 - a. The tests for sucrose and polysorbate should be added to the tests and specifications for the drug product.
 - b. The content uniformity of the drug product should be determined based on potency, not weight variation.
 - c. A limit of NMT % for oxidized α -subunit as listed in your current tests and specifications for the drug product (Vol. 4.2, Attachments XA and XB, pages 282-292) is unacceptable. Based on the stability data provided in Vol. 4.3, Attachment XIID, pages 76-80, a much lower level of oxidation occurred in the product stored at 2-8°C. The specification for the oxidized recFSH should be revised according to the results obtained from samples stored at 2-8°C.
 - d. A revised tests and specification sheet, including all the changes recommended previously, and in this letter must be submitted. In addition, the new tests for oxidized FSH and protein content should be submitted when validation of these methods is completed.
 - e. The batch/lot numbers and the manufacturing dates for the ten lots of recFSH which were analyzed by as shown in the photographs submitted in the amendment dated March 11, 1997, should be submitted.
2. Stability
 - a. Based on the stability data provided in Vol. 4.3, Attachment XIID, pages 77-88 for the oxidized recFSH, the proposed storage condition of 2-30°C and a 24-month expiration dating are not acceptable. Although the oxidized FSH may be biologically active, it is still considered a degradation product. In addition, a preparation containing % of oxidized form as indicated in the tests and specification section would make it a product chemically different from the authentic FSH. Your stability data has indicated that a much lower level of oxidation occurred in samples stored at 2-8°C; therefore, it is a

- more appropriate storage condition for the drug product. Accordingly, the storage conditions printed in the **HOW SUPPLIED** section of package insert should be revised.
- b. A statement indicating the percentage of oxidized recFSH and the effect of oxidation on the biological activity should be added to the **DESCRIPTION** section of package insert if a limit larger than % is proposed.
 - c. The stability data (Vol. 4.3, Attachment XIIF, pages 108-111) have shown an increase in the sialic acid content at the 18-month testing interval for all four lots of drug products. Please explain.
 - d. The stability results of sialic acid content (Vol. 4.3, Attachment XIIF, pages 108-111) are presented in nanomoles, not a relative ratio to mannose as listed in the Tests and Specification section. Since sialic acid content is a part of stability testing, the test should be revised so that the result can be presented as a relative ratio to mannose.
 - e. In our letter dated December 5, 1996, we requested that the representative be submitted as part of stability results for samples tested at different intervals. To date, these data have not been provided.
 - f. Your post-marketing stability protocol should be revised to include all the additional tests with proper specifications as requested in our letter dated December 5, 1996, and to change the storage temperature to 2-8°C. The revised protocol should be provided for review as soon as possible.
 - g. For your future stability report, all the data should be tabulated and presented in a single table. The current format, that contains partial results in a table supplemented with additional data in separate attachments, is not acceptable.

Other

Additional deficiencies have been sent, under separate cover, to the holder of DMF. Correction of those deficiencies is required prior to NDA approval.

Nomenclature

You have proposed the established name for your product as "follitropin beta." The Center has several concerns regarding the proposed "beta" suffix as part of the established name. We will keep you informed as discussions regarding the established name for this product continue.

Labeling

General

The proposed alternate tradename. _____ has been found unacceptable by the CDER Labeling and Nomenclature Committee because of its similarity to other products.

Package Insert

See enclosed. Please note, additional revisions of this labeling may be required upon receipt and review of your response.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Lana L. Pauls, M.P.H., Chief, Project Management Staff, at (301) 827-4260.

Sincerely,



Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Revised labeling

Name	Title	Signature	Date
Lana L. Pauls, M.P.H.	Chief, Project Management Staff	<i>Lana L. Pauls</i>	4/10/97
Ridgely Bennett, M.D., M.P.H.	Medical Officer	<i>Ridgely C. Bennett</i>	4/10/97
Heidi Jolson, M.D., M.P.H.	Deputy Director	<i>Heidi Jolson M.D.</i>	4/10/97
Duu-Gong Wu, Ph.D.	Chemist (HFD-510)	<i>Duu-Gong Wu</i>	4/10/97
Moo-Jhong Rhee, Ph.D.	Chemistry Team Leader	<i>Moo-Jhong Rhee</i>	4/10/97
Krishan Raheja, D.V.M., Ph.D.	Pharmacologist	<i>Krishan R. Raheja</i>	4/10/97
Alexander Jordan, Ph.D.	Pharmacology Team Leader	<i>A. Jordan</i>	4/10/97
K. Gary Barnette, Ph.D.	Pharmacokineticist	<i>K. Gary Barnette</i>	4/10/97
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader	<i>Dorantes</i>	4/10/97
Joy Mele, M.S.	Statistician (HFD-510)	<i>Joy Mele</i>	4/10/97
Kate Meaker, M.S.	Statistician	<i>Kate Meaker</i>	4/10/97
Lisa Kammerman, Ph.D.	Statistical Team Leader	<i>Lisa Kammerman</i>	4/10/97
Lisa Rarick, M.D.	Director	<i>Lisa Rarick</i>	4/10/97

cc:

- Original NDA 20-582
- HFD-580/Div. files
- HFD-002/ORM
- HFD-102/Office Director
- HFD-101/L. Carter
- HFD-820/ONDC Division Director
- DISTRICT OFFICE
- HFD-92/DDM-DIAB
- HFD-580/L. L. Pauls
- HFD-580:

Drafted by: LPauls/April 9, 1997/N20582NA.001

Initialed by:

final:

LLP 4/10/97

NDA 20-582

Page 6

NOT APPROVABLE (NA)

NDA 20-582
Follistim™ [follitropin beta (rDNA origin) for injection]
Serono Laboratories, Inc.

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-582
Follistim™ [follitropin beta (rDNA origin) for injection]
Serono Laboratories, Inc.

Federal Register Notices

This application was not the subject of any Federal Register Notices.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-582 Trade (generic) names FOLLISTIM (FOLLITROPIN)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&W studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

NDA 20-582
Follistim™ [follitropin beta (rDNA origin) for injection]
Serono Laboratories, Inc.

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

Group Leader Memorandum

SEP 26 1997

NDA: 20-582

Drug and indication: Follistim® (follitropin beta for injection) for the
1) development of multiple follicles in ovulatory patients
participating in an Assisted Reproductive Technology (ART)
program, and 2) induction of ovulation and pregnancy in
anovulatory infertile patients in whom the cause of infertility
is functional and not due to primary ovarian failure.

Dosage form/Route: 75 IU and 150 IU/vials via subcutaneous or intramuscular
injection

Applicant: Organon, Inc.

Submission dated: January 10, 1996 (original NDA)
May 14, 1997 (response to April 10, 1997 not approvable
letter)

Date of MO review: March 18, 1997

Date of Memorandum: September 26, 1997

In this application, the sponsor requests approval for human follicle-stimulating hormone (FSH), which is manufactured by recombinant DNA technology, for use as part of ART and ovulation induction procedures. In support of these two indications, the sponsor has submitted the results of four controlled clinical trials that compared the safety and efficacy of follitropin beta with either Metrodin® or Humagon™. The results of these studies suggest that follitropin beta is comparable in safety and efficacy to the comparator products.

Because of significant deficiencies encountered during the inspection of one of the manufacturing facilities, a not approvable letter for the original application was issued on April 10, 1997. The resubmission on May 14, 1997 and subsequent amendments satisfactorily address the deficiencies noted in the not approvable letter. I concur with the recommendation of the primary reviewers that this application is now approvable. However, several aspects of this drug's approval merit comment:

1. Comparability with urinary-derived FSH products

During labeling negotiations, the sponsor asserted that the clinical trials for ART demonstrated that follitropin beta was therapeutically superior to the comparator products. This claim was based on the finding of a small, but statistically significant difference in the mean number of oocytes recovered between the two treatment groups.

However, the final labeling will reflect the consensus of the review team that the efficacy of follitropin beta is comparable to either Metrodin® or Humagon™ because: there were no differences between groups in the more clinically important parameter of pregnancy rate; the efficacy of these products is highly variable depending on the patient and the doses used; and the finding of a somewhat higher rate of Ovarian Hyperstimulation Syndrome in the follitropin beta group (5.2% vs. 4.3%) suggests that higher numbers of follicles are not always desirable.

2. Nomenclature

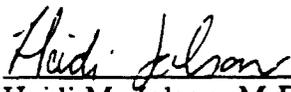
The sponsor has requested the generic product name, follitropin beta, to be consistent with their already marketed product name in Europe. This request was problematic because another recombinant FSH product, which is believed to be chemically and clinically indistinguishable, has requested the generic name of follitropin alfa. After considerable internal deliberation and discussion with the USAN council, it was decided to allow the requested generic name, although it was agreed that a single, uniform generic name would have been preferable. In order to minimize any possible confusion, the product labeling will clearly state that follitropin beta and alfa are chemically indistinguishable. Further measures to reduce any negative impact of the nomenclature decision are summarized in Dr. Wu's memorandum.

3. Safety

The principle safety issues, Ovarian Hyperstimulation Syndrome and the risk of multiple births, are expected adverse events with products in this class and are adequately described in the product label.

4. Phase IV commitments

Phase IV commitments related to chemistry, manufacturing and controls. were made in amendments dated May 14 and June 30, 1997, and are summarized in Dr. Wu's memorandum.



Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-582
HFD-580/LRarick/RBennett/HJolson

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Consult #535 (HFD-510)

FOLLISTIM

recombinant follicle stimulating hormone, sterile lyophilized
cake for injection

The syllable "stim" in the trademark is a USAN stem syllable for colony stimulating factors therefore its use in trademarks is to be discouraged.

The Committee finds the proposed trademark to be unacceptable for the above listed reason.

CDER Labeling and Nomenclature Committee

 _____, Chair

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of *metabolism Drug product* HFD-510

Attention: *Duu-Gong Wu, Ph.D.* Phone: 443-3520

Date: *11/4/96*

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: *PREGON* NDA/ANDA# *20-580*

Established name, including dosage form:

*Follitropin beta for injection, (lyophilized powder).
also called recombinant human follicle stimulating hormone.

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):

*Stimulation of multiple follicular growth for
women undergoing in vitro fertilization.*

Initial Comments from the submitter (concerns, observations, etc.):

*The applicant has previously submitted a trademark
"Follistin" for this product. Because US trademark office has
not acted on that proposal, the applicant would like to have
the "PREGON", already approved by the Trademark Office, to be considered*

Note Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit *as an*
this form at least one week ahead of the meeting. Responses will be as timely as possible *alternate*

SEP 29 1997

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 29, 1997

FROM: Duu-Gong Wu, Ph.D. Chemistry Team Leader II, DNDC II

Duu-Gong Wu 9/29/97

SUBJECT: Carton and vial labels

TO: NDA 20-582, Follistim(follitropin beta for injection)

In the review of carton and vial labels for the drug product included in the amendment dated 6/12/97, the picture printed on the carton labels was found unacceptable by the Division of Drug Marketing, Advertising and Communications. The applicant has been requested in a letter dated 8/15/97 to remove the picture. The final draft carton and vial labels received by fax on 9/29/97 show that the picture has been removed. Also, according to our previous requests, the established name and the storage conditions printed on the labels have been revised to read

Conclusion

The carton and vial labels are now acceptable.

CC:
Original NDA 20-582
HFD-580/Divisional File
HFD-510/DG Wu
HFD-580/MJ Rhee/L. Pauls