

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-149

CHEMISTRY REVIEW(S)

SEP 15 2000

Addendum to Summary of Chemistry Review of NDA 21-149

Microbiology review #1 indicated that from microbiology perspective, the NDA can be approved, however, it also indicated that several comments should be conveyed to the sponsor. Those comments are not approvability issues, however, they are to advice the firm to include certain information in the microbiology section of the future applications to help the Agency review the applications more effectively.

The letter was issued as a general correspondence on September 14, 2000.

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

cc: original NDA 21-149
HFD-580/Div File
HFD-580/MRhee
HFD-510/DWu/YYang
HFD-820/JGibbs/SKoepeke

The lyophilized powder is packaged into a glass vials with which is sealed with an . The container closure system is deemed suitable for protection of the product during the shelf-life.

Based on available primary as well as supportive stability data, 24-month of expiry date is granted. The reconstituted solution is stable for 24 hours at 25oC.

The tradename, Ovidrel, was accepted by OPDRA and the established name, choriogonadotropin alfa, was also accepted by USAN. All other labeling as well as labels are deemed in compliance to the labeling requirements.

Conclusion and Recommendation:

As recommended from Chemistry Review #2, this NDA can be approved from chemistry, manufacturing, and controls point of view.

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

cc: original NDA 21-149
HFD-580/Div File
HFD-580/MRhee
HFD-510/DWu/YYang
HFD-820/JGibbs/SKoepeke

MEMORANDUM

Date: September 13, 2000
TO: NDA # 21-149, Ovidrel®, Sorono Laboratories, Inc.
From: Yvonne Yang, Ph.D., Chemist Reviewer, HFD-510
Subject: Clarification for attached Draft Deficiency Letter in
Chemistry Review #1 and USAN name

151
19-13-00
/S/

This memo is to provide a clarification for pp. 87-88 of chemistry review #1 containing a draft deficiency letter that was forwarded to the applicant on 7-31-00. All deficiencies in the letter have been addressed in the amendments dated 8-7-00, 8-28-00, and 8-29-00. The responses have been reviewed along with the relevant sections and found satisfactory (see chemistry review #1). The inclusion of the Draft Deficiency Letter in Chemistry Review #1 is for the purpose of record keeping.

According to the information provided by the applicant, the non-proprietary name, choriogonadotropin alfa, has been adopted by the USAN Council as the United States Adopted Name for Ovidrel®.

Cc: NDA # 21-149
HFD-580/Division File
HFD-510/YYang/DGWu
HFD-580/MJRhee/EDeGuia

SEP 11 2000

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

| | | | |
|------------------------|----------------------|------------------------------|----------------------|
| <u>NDA #:</u> 21-149 | <u>REVIEW #:</u> 2 | <u>REVIEW DATE:</u> 09-11-00 | |
| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
| Original | 11-23-99 | 11-26-99 | |
| Amendment | 08-28-00 | 08-29-00 | |
| Amendment | 08-29-00 | 08-31-00 | |
| Amendment | 09-06-00 | 09-07-00 | |

NAME & ADDRESS OF APPLICANT: Sorono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

DRUG PRODUCT NAME:

Proprietary: Ovidrel®
Non-Proprietary: Choriogonadotropin alfa
Established: Choriogonadotropin alfa
Common Name: Recombinant human chorionic gonadotropin(r-hCG)
Code Name/#: r-hCG: CAS-177073-44-8
(Alpha subunit: CAS-56832-30-5)
(Beta subunit: CAS-56832-34-9)
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION:

See chemistry review #1

DOSAGE FORM:

Lyophilized powder for injection

STRENGTHS:

250 mcg/vial

ROUTE OF ADMINISTRATION:

Subcutaneous

Rx/OTC:

X Rx OTC

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

See chemistry review #1

REMARKS:

This review covers amendments dated 8-28-00, 8-29-00, and 9-06-00. The amendment dated 8-28-00 provides for the revised specification for the bioidentity assay in the stability protocol for all future time points of the ongoing and post-approval studies (also see comments on pp. 77, 79 from review #1). The amendment dated 8-29-00 provides (1) the revised specifications for drug substance including a test for ~~_____~~ and a full bioassay, (2) letter of authorization from ~~_____~~ for DMF ~~_____~~ for the stoppers (also see comments on pp. 62 from review #1). A copy of the revised drug substance specifications is attached. The amendment dated 9-06-00 provides for the withdrawal of the alternate packaging facility in ~~_____~~ from this NDA.

Microbiology consult review is completed. Microbiology recommends APPROVAL for this NDA with minor comments for future applications (see microbiology review for details).

CONCLUSIONS & RECOMMENDATIONS:

Adequate information has been provided. From a chemistry point of view, this application can be approved.

cc:

Org. NDA 21-149

HFD-580/Division File

HFD-510/YYang/DGWu

HFD-580/EDeGuia/MRhee

R/D Init. by:

/S/

Yvonne Yang, Ph.D.
Review Chemist

/S/

HFD-580/DeGuia

AUG 25 2000

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

| | | | |
|-------------------------------|-----------------------------|---------------------------|-----------------------------|
| <u>NDA #:</u> 21-149 | | <u>REVIEW #:</u> 1 | <u>REVIEW DATE:</u> |
| <u>SUBMISSION TYPE</u> | <u>DOCUMENT DATE</u> | <u>CDER DATE</u> | <u>ASSIGNED DATE</u> |
| ORIGINAL | 11-23-99 | 11-26-99 | 12/02/99 |
| Amendment | 06-26-00 | 06-27-00 | |
| Amendment | 08-07-00 | 08-08-00 | |
| Amendment | 08-29-00 | | |

NAME & ADDRESS OF APPLICANT: Sorono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

DRUG PRODUCT NAME:

Proprietary: Ovidrel®
Non-Proprietary: Choriogonadotropin alfa
Established: Choriogonadotropin alfa
Common Name: Recombinant human chorionic gonadotropin(r-hCG)
Code Name/#: r-hCG: CAS-177073-44-8
(Alpha subunit: CAS-56832-30-5)
(Beta subunit: CAS-56832-34-9)
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY/INDICATION:

Induction of final follicular maturation and early luteinization in infertile women who have been appropriately pretreated with follicle stimulating hormones as part of an ART program, or under controlled ovarian stimulation for treatment of anovulation which is _____ and not due to primary ovarian failure.

DOSAGE FORM: Lyophilized powder for injection
STRENGTHS: 250 mcg/vial
ROUTE OF ADMINISTRATION: Subcutaneous
Rx/OTC: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Recombinant human chorionic gonadotropin (r-hCG)

See also Chemist's Review Notes.

REMARKS:

This is a consult review for HFD-580. Ovidrel® is a product of recombinant human chorionic gonadotropin (r-hCG). Human chorionic gonadotropin (hCG) consists of two polypeptide subunits (alpha and beta) bound together non-covalently. r-hCG is produced in genetically engineered Chinese Hamster Ovary (CHO) cells in which the genes encoding for the alpha and beta subunits of hCG were introduced through recombinant DNA technology. During the production phase, r-hCG is secreted into the culture media and subsequently _____ chromatography.

Ovidrel® is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (1 ml). Each vial of Ovidrel® when reconstituted will deliver either 250 µg (equivalent to 5,000 USP IU) of r-hCG. The vials are filled with either 285 µg of drug substance to compensate for the volume loss (caused by dead space) in order to deliver the intended 250 µg of active ingredient in a withdrawn volume of less than 1 ml.

The vials are filled based _____ traditionally used for the manufacturing of gonadotropin drug products (e.g. FSH, hCG). This will assure a more precise dosing and avoid the variation in different batches due to low precision of the bioassay. The

The amendment dated 6-26-00 provides for bioassay data and updated stability data. Amendments dated 8-7-00 and 8-29-00 provide responses to CMC information request in a letter dated 7-31-00 and in a teleconference on 8-17-00. One of the manufacturing facilities for an alternate diluent and an alternate packaging facility included in the original submission have been withdrawn (amendment dated 8-3-00). The remaining three manufacturing facilities have been inspected and found acceptable (see attached EES printouts). Tradename consult is completed, and OPDRA does not have any objection to the use of the proprietary name, Ovidrel®. Microbiology consult is still pending. The comments related to package insert and container labels have been forwarded to the applicant for revision.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry point of view, this submission is approvable pending a satisfactory consult review from the Microbiologist, and a minor revision for the _____ test for the release of the drug substance.

cc:
Org. NDA 21-149
HFD-580/Division File
HFD-510/YYang/DGWu
HFD-580/EDeGuia/MRnee
R/D Init. by:

/S/

/S/

Yvonne Yang, Ph.D.
Review Chemist

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21149/000
Stamp: 24-NOV-1999
Regulatory Due: 24-SEP-2000
Applicant: SERONO LABS
100 LONGWATER CIR
NORWELL, MA 02061
Priority: 3S
Org Code: 580

Action Goal:
District Goal: 26-JUL-2000
Brand Name: OVIDREL (CHORIOGONADOTROPIN ALFA) 250
Estab. Name:
Generic Name: CHORIOGONADOTROPIN ALFA
Dosage Form: (FOR INJECTION)
Strength: 250 MCG

Application Comment: RECOMBINANT HUMAN CHORIONIC GONADOTROPIN

(on 21-JAN-2000 by Y. YANG (HFD-820) 301-827-6421)

FDA Contacts: E. DEGUIA (HFD-580) 301-827-4260 , Project Manager
Y. YANG (HFD-820) 301-827-6421 , Review Chemist
D. WU (HFD-510) 301-827-6375 , Team Leader

Overall Recommendation: ACCEPTABLE on 21-AUG-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

WITHHOLD on 21-AUG-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:

DMF No: AADA:

Responsibilities:

Profile:

Estab. Comment:

(on 30-MAR-2000 by Y. YANG (HFD-820) 301-827-6421)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|---------------------|-------------|-----------|------------|-------------------|-----------|
| SUBMITTED TO OC | 30-MAR-2000 | | | | YANGY |
| SUBMITTED TO DO | 31-MAR-2000 | 10D | | | FERGUSONS |
| ASSIGNED INSPECTION | 05-APR-2000 | PS | | | CEVERLY |
| DO RECOMMENDATION | 10-APR-2000 | | | ACCEPTABLE | CEVERLY |

BASED ON FILE REVIEW

RECOMMENDS APPROVAL FOR THE FIRM'S ROLE IN THE MANUFACTURE OF NDA 21-149 SPONSORED BY SERONO LABS. THIS RECOMMENDATION IS BASED ON A FILE REVIEW AND THE LAST INSPECTION WHICH WAS CONDUCTED 2/00.

OC RECOMMENDATION 10-APR-2000

ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

Establishment:

DMF No: AADA:

Responsibilities:

Profile: OAI Status: NONE

Estab. Comment:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

(on 21-JAN-2000 by Y. YANG (HFD-820) 301-827-6421)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|----------------------|-------------|-----------|-------------|--------------------------|---------|
| SUBMITTED TO OC | 21-JAN-2000 | | | | YANGY |
| SUBMITTED TO DO | 24-JAN-2000 | GMP | | | EGASM |
| ASSIGNED INSPECTION | 24-JAN-2000 | GMP | | | EGASM |
| INSPECTION SCHEDULED | 24-FEB-2000 | | 12-MAY-2000 | | IRIVERA |
| INSPECTION PERFORMED | 15-JUN-2000 | | 12-MAY-2000 | | EGASM |
| DO RECOMMENDATION | 27-JUN-2000 | | | ACCEPTABLE | EGASM |
| OC RECOMMENDATION | 27-JUN-2000 | | | INSPECTION ACCEPTABLE | EGASM |
| | | | | DISTRICT RECOMMENDATION | |

Establishment: 9692032

LABORATORIOS SERONO SA
AUBONNE, , SZ

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile:

CBI

OAI Status: NONE

Estab. Comment: INSPECT SITE OPERATIONS FOR PRODUCTION

PROCESS LABORATOIRES SERONO S.A. (LSA), ZONE
INDUSTRIELLE DE L'OURIETTAZ

1170 AUBONNE, SWITZERLAND (on 21-JAN-2000 by Y. YANG (HFD-820)
301-827-6421)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|----------------------|-------------|-----------|-------------|--------------------------|---------|
| SUBMITTED TO OC | 21-JAN-2000 | | | | YANGY |
| SUBMITTED TO DO | 24-JAN-2000 | GMP | | | EGASM |
| ASSIGNED INSPECTION | 24-JAN-2000 | GMP | | | EGASM |
| INSPECTION SCHEDULED | 28-APR-2000 | | 15-JUN-2000 | | IRIVERA |
| INSPECTION PERFORMED | 19-JUN-2000 | | 15-JUN-2000 | | IRIVERA |
| DO RECOMMENDATION | 27-JUN-2000 | | | ACCEPTABLE | EGASM |
| OC RECOMMENDATION | 27-JUN-2000 | | | INSPECTION ACCEPTABLE | EGASM |
| | | | | DISTRICT RECOMMENDATION | |

Establishment: 1220970

SERONO LABORATORIES INC
62 & 76 PACELLA PARK DR
RANDOLPH, MA 02368

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile:

SVS

OAI Status: NONE

Estab. Comment: INSPECT SITE OPERATIONS FOR ALTERNATIVE PACKAGING FACILITY

SERONO LABORATORIES, INC.

62 PACELLA PARK DRIVE, RANDOLPH, MA 02368, USA (on 21-JAN-2000 by
Y. YANG (HFD-820) 301-827-6421)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|--------------------------|------------|
| SUBMITTED TO OC | 21-JAN-2000 | | | | YANGY |
| OC RECOMMENDATION | 24-JAN-2000 | | | WITHHOLD | DAMBROGIOJ |
| | | | | FACILITY OUT OF BUSINESS | |

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Method Validations

A Method Validation Package will be prepared and samples of the drug substance and drug product will be requested so that the FDA laboratories can evaluate the methods. See Chemistry Review, Method Validation, page 83 for details.

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

CAC/ECC Report

Not Applicable.

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Environmental Assessment Review

Pursuant to CFR 25.31 (a) Serono Laboratories, Inc. claims categorical exclusion for the preparation and submission of an Environmental Assessment (Volume 2.11, page 394 of the NDA).

ENVIRONMENTAL RISK ASSESSMENT

The active medicinal moiety in Ovidre!® is choriogonadotropin alfa. Choriogonadotropin alfa is produced by mammalian cells (Chinese hamster ovary cells) into which a recombinant DNA expression cassette has been inserted. Under controlled _____ conditions choriogonadotropin alfa is expressed by CHO cells. The active moiety is harvested from the _____ for subsequent preparation into a suitable formulation for injection.

The primary structure of choriogonadotropin alfa is identical to human chorionic gonadotropin (hCG), a naturally occurring human protein that is derived from the urine of pregnant women and that is currently sold in the U.S. by Serono under the brandname, Profasi®. Thus, pursuant to 21 CFR 25.31(a) Serono Laboratories, Inc. claims categorical exclusion for the preparation and submission of an Environmental Assessment.