CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-149

ADMINISTRATIVE DOCUMENTS

13. PATENT INFORMATION

The following patent information is provided in accordance with the Drug Price and Patent Term Restoration Act of 1984:

Tradename:	Ovidrel®
Active Ingredient:	Choriogonadotropin alfa (r-hCG)
Strengths:	250 mcg
Dosage Form:	lyophilized powder for injection

Patent Information

U.S. Patent Number: US Patent 5,767,251

(Recombinant Gonadotropins, including r-hCG)

Expiration Date:	June 16, 2015
Type of Patent:	Drug Substance Patent
Name of Patent Owner:	Genzyme Corporation

U.S. Patent 5,767,251 was issued in the name Genzyme Corporation, the successor to Integrated Genetics, Inc. Pursuant to the Purchase and License Agreement between Integrated Genetics, Inc. and Ares-Serono, Inc. of June 6, 1989, U.S. Patent 5,767,251 remains the property of Integrated Genetics, Inc. or its successors but Ares-Serono, Inc. and its affiliates, including Serono Laboratories, Inc., have a worldwide, exclusive irrevocable royalty-free license to this patent.

14. PATENT CERTIFICATION

Pursuant to 21 U.S.C. Section 355(b)(1), Serono Laboratories, Inc. has reviewed the records of the U.S. Patent and Trademark Office and is of the opinion that there are no United States patents to which Serono Laboratories, Inc. does not have a license which claim recombinant human Chorionic Gonadotropin (r-hCG) or a method of using r-hCG with respect to which a claim of patent infringement could reasonably be asserted against Serono Laboratories, Inc. in connection with the manufacture, use or sale of r-hCG for the treatment of patients with Female Infertility.

19. MARKET EXCLUSIVITY

Serono Laboratories, Inc. claims five years product market exclusivity pursuant to Section 505(c)(3)(D)(ii) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.108(b)(2). Serono Laboratories Inc. has reviewed the 19th Edition (and corresponding supplements) of the list of Approved Drug Products with Therapeutic Equivalence Evaluations (including list of discontinued products) to determine whether the U.S. Food and Drug Administration has previously approved any New Drug Application under Section 505(b) of the Act containing the active moiety, choriogonadotropin alfa. Based on its review of the Orange Book and to the best of its knowledge, Serono Laboratories Inc. does not believe that the U.S. Food and Drug Administration has previously approved any New Drug Application for a product(s) containing the active moiety, choriogonadotropin alfa.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 21-149

Trade Name: Ovidrel® **Generic Name: choriogonadotropin alfa for injection**

Applicant Name: Serono Laboratories, Inc. **HFD # 580**

Approval Date If Known: September 20, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. **An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.**

   a) **Is it an original NDA?**

   YES/_X__/ NO /_ _/

   b) **Is it an effectiveness supplement?**

   YES /_ _/ NO /_X__/

   If yes, what type? (SE1, SE2, etc.) _SE1_____

   c) **Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")**

   YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /__ _/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____5 Years_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_ X__/ NO /__ _/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 20-378 Gonal-F (follitropin alfa for injection) and NDA 20-582 Follistim (follitropin beta for injection) _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X _/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X __/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_ __/ NO /_ X__/

(1) **If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.**

YES /___/ NO /_X_ _/

If yes, explain:

(2) **If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?**

YES /___/ NO /_ X__/

If yes, explain:

(c) **If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: Clinical Trials 7927, 7648 and 8209**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. **In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.**

a) **For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")**

Investigation #1 YES /_ __/ NO /_X __/

Investigation #2 YES /_ __/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____

b) **For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?**

Investigation #1 YES /___/ NO /_ X__/

Investigation #2 YES /___/ NO /_X _/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

(c) **If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):**

_Study 7927_____Study 8209_____

_Study 7648_____ _____

4. **To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.**

a) **For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?**

Investigation #1

IND # 48,934___ YES /__X_/ NO /___/ Explain: _____

Investigation #2

IND # _48,934____ YES /_X__/ NO /___/ Explain: __ _____

Investigation #3

IND # 48,934 _____YES *X*___/NO/ ___/ Explain:_____

b) **For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?**

Investigation #1

YES /___/ Explain _____ NO /___/ Explain __N/A_____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain ___N/A_____

_____ _____

_____ _____

(c) **Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)**

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature: /S/ **Date:** 9/20/2000

Title: Regulatory Project Manager

Signature of Office/Division Director

Signature: /S/ **Date:** 9/20/00

cc: Original NDA Division File
HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021149	**Trade Name:**	OVIDREL(CHORIOGONADOTROPIN ALFA)250,
Supplement Number:	000	**Generic Name:**	CHORIOGONADOTROPIN ALFA
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF
Action Date:	~~11/24/99~~ 09-20-00		

Indication # 1	Induction of final follicular maturation and early luteinization in infertile women undergoing Assisted Reproductive Technology.
Label Adequacy:	Does Not Apply
Forumulation Needed:	NO NEW FORMULATION is needed
Comments (if any):	The drug has no potential use in pediatric patients. Sponsor requested a pediatric waiver.

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	9/20/00

Comments: The drug is not indicated for use in pediatric patients.

This page was last edited on 9/20/00

/S/ — Signature

9-20-2000 — Date

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Certification Statement for Waiver of Requirement for Conducting Pediatric Studies

In accordance with 21 CFR 314.55(c)(2), the undersigned hereby certifies the following:

The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

Not applicable

Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

Not applicable

There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

Not applicable

Pamela Williamson Joyce
Vice President Regulatory Affairs

8/29/00
Date

ES-SERONO GROUP

BELGIUM
BRAZIL
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COLOMBIA
COMMONWEALTH OF RUSSIA
FRANCE
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SPAIN
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U K
URUGUAY
USA
VENEZUELA

Serono
PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

ORIGINAL

August 29, 2000

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug
Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

NDA 21-149
Ovidrel® (choriogonadotropin alfa)
Request for Full Waiver of Requirement for Conducting Pediatric Studies

Dear Dr. Allen:

Reference is made to NDA 21-149 for Ovidrel® (choriogonadotropin alfa) submitted on November 23, 1999. Further reference is made to an August 23, 2000 teleconference with the Agency during which a request for a full waiver of the requirement for conducting pediatric studies was requested.

In accordance with 21 CFR 314.55 (c)(2), Serono respectfully requests a full waiver of the requirement for conducting pediatric studies with Ovidrel®. Since Ovidrel® is indicated for the treatment of infertile women, its administration in the pediatric population is not warranted. A certification statement is attached.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns regarding this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate or the undersigned at (781) 982–9000.

Yours sincerely,

for P.W.J.

Pamela Williamson Joyce
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N/A ☐ MEMO
CSO INITIALS DATE

16. DEBARMENT CERTIFICATION

Debarment Certification Statement

In accordance with Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned hereby certifies that Serono Laboratories, Inc. did not and will not use in any capacity the services of any person debarred under sections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Rosann J. Reinhart
Executive Director, Regulatory Affairs

23-Nov-99
Date

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Serono Laboratories

Advisory Committee Meeting Minutes

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

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Serono Laboratories

Federal Register Notices

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

18 USER FEE

Serono Laboratories, Inc. has submitted check 37912 for $272,82 as payment for the review of this original New Drug Application. Please refer to the following cover letter, User Fee Cover Sheet and photocopy of the check sent to the US Food and Drug Administration's lockbox at the Mellon Bank located in Pittsburgh, PA.

NDA 21,149
Ovidrel

September 20, 2000

Memorandum to the File

Table 7 of the labeling being approved has slightly different numbers from those listed for Ovidrel in Table 9 of my review because the outcome of the one ongoing pregnancy listed in my Table 9 for Ovidrel is now known to be a single live birth. The updated table as it appears in the labeling is shown below.

Table 7: Pregnancy Outcomes of r-hCG in OI (Study 8209)

Parameter	Ovidrel® 250 mcg (n = 22)
Clinical pregnancies not reaching term	7 (31.8%)
Live Births	15 (68.2%)
Singleton	13 (86.7%)
Multiple birth	2 (13.3%)

The outcomes of 4 ongoing pregnancies treated with Profasi is now also known. There were three single live births and one twin live birth.

There were no congenital anomalies in any of these pregnancies.

/S/

Ridgely C. Bennett, M.D., M.P.H.

Confidential

serono

September 20, 2000

Susan Allen, M.D.,
Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Tel: 781-982-9000
Fax: 781-871-6754
www.seronousa.com

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Information Request: Final Package Insert

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Reference is also made to correspondence from the Division on Septemeber 19, 2000 whereby edits and comments to the draft package insert were made (Attachment 1).

Herewith, please find the final package insert. For your convenience, the label is provided in both paper and electronic formats.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

Enclosure: diskette
cc: Eufrecina DeGuia (Desk Copy)

Memo

For: NDA 21-149, Ovidrel
From: Karen L. Davis-Bruno; Ph.D. /S/ 9/19/00
Re: Revised Pregnancy Labeling for NDA 21-149
Date: 9/19/00

Previous draft labeling was based on a _____ Since the approvable human dose of Ovidrel is 250 mcg, the pregnancy labeling should be modified to reflect this change as follows: " Fetal death and impaired parturition were observed in pregnant rats given a dose of hCG (25 mcg) equivalent to six times the human dose of 250 mcg" . See Line 277-279. This has been addressed satisfactorily in the labeling comments sent to the sponsor 9/19/00.

MEMORANDUM

Date: September 15, 2000

To: Shelley Slaughter, M.D.
Team Leader, HFD-580

From: Lisa Stockbridge, Ph.D. (Regulatory Reviewer, DDMAC) LS

Re: Comments on proposed labeling for Ovidrel

I have reviewed the proposed labeling for Ovidrel and have the following comments:

1. The term "statistically equivalent" is confusing. If the product comparison was statistically significant and clinically significant, both parameters should be stated.

2. It is understood that the number of "live births" means the number of gestations, not the number of infants. If this is not so, the terminology should be made clearer.

3. The directions for injection should begin with "Wash hands thoroughly with soap and water."

4. The diluent should be defined as "sterile water" the first time the term is used (line 364). After that the terminology should remain consistent (i.e., either use "diluent" or "sterile water").

5. The figure for Step 2 shows only injection

6. The figure for Step 3 does the wording "straight, upright position."

7. In Step 6 and Step 9, use the term "push"

8. For consistency, in Step 8 use the term "wipe" (line 393).

ORIGINAL

SERONO, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061
(781) 982-9000 TEL.
(781) 878-5001 FAX.

ORIG AMENDMENT

BM

FACSIMILE TRANSMITTAL SHEET

TO: FRESHNIE DEGUIA	FROM: PAMELA WILLIAMSON JOYCE
COMPANY: US FOOD AND DRUG ADMINISTRATION	DATE: SEPTEMBER 15, 2000
FAX NUMBER: 301-827-4267	TOTAL NO. OF PAGES INCLUDING COVER: 2
PHONE NUMBER: 301-827-4260	SENDER'S REFERENCE NUMBER:
RE: OVIDREL 21-149 RESPONSE TO REQUEST	YOUR REFERENCE NUMBER:

☐ URGENT ☑ FOR REVIEW ☐ PLEASE COMMENT ☐ PLEASE REPLY ☐ PLEASE RECYCLE

NOTES/COMMENTS:

Freshnie:

Enclosed please find a copy of the e-mail I recently sent you in response to a request for information for Ovidrel NDA 21-149.

Please call me at (781) 681-2298 should you have any questions.

Best Regards,

Pamela Williamson Joyce

Serono

From: Pamela Williamson/US_BOS01/SERONO on 09/15/2000 12:07 PM

To: deguiae@cder.fda.gov
cc: Debbie DeMuria/US_BOS01/SERONO@SERONO
bcc:
Del. date:
Ref. No: PWIN/4P7N2C
Subject: Ovidrel 21-149 Response to Request for Information

Freshnie, here are the responses to the two questions received today. Please confirm receipt.

1) number and percentage of subjects with ALT rise after correction for pre-existing conditions in the 500 mcg group and the total "n"

- **There were 9 patients (out of 89) who had elevated ALT in the 500 mcg Ovidrel group. As indicated in Lines 234 of the PI, there were 10 (3%) of 335 Ovidrel 250 mcg patients who had elevated ALT. Therefore, the total number of Ovidrel patients (i.e., including 500 mcg Ovidrel) who had Elevated ALT becomes 19 and the percentage would be 4.5% (i.e., (10+9)÷ (335+89)= 19÷424=4.5%).**

2) how we constructed the total "n"s for 250 mcg, 500 mcg and urinary groups and the studies that were included in order to verify the numbers in the Precaution section of the PI (i.e., 335 Ovidrel, 328 urinary)

Study	250 mcg Ovidrel	500 mcg Ovidrel	U-hCG
ART -- 7927	95	89	96
ART -- 7648	97		93
ART -- 9073	44		40
OI -- 8209	99		99
Total	335		328

Please do not hesitate to contact me if additional information is required.

Best regards,

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-149

Serono Laboratories
Attention: Pamela Williamson-Joyce
Vice President, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

SEP 14 2000

Dear Ms. Williamson-Joyce:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ovidrel® (choriogonadotropin alfa) 250 mcg.

We have completed review of the Microbiology section of your submission and have no comments regarding this application. However, to assist you in filing more complete information in future applications for sterile products, please be advised of the following:

1. Media fill procedures (volume 11, page 59 and [redacted]) did not address simulations of the lyophilization step. For lyophilized products, this critical part of the [redacted] process should be included in the validation and discussed in the application.

2. Details of the container and closure integrity test (volume 11, page 68) were incomplete. It is customary to provide the number of units tested, dates of tests, media controls (i.e., growth promotion) and whether the closure was in contact with the medium during or after the challenge.

3. For the vials containing WFI (Water for Injection) as a solvent (as described in your amendment dated June 16, 2000) the alert limit for bioburden [redacted] (section 3.4 on page 14). Since the bulk solution is WFI, for which a generally accepted Action Limit is [redacted] the proposed limit should be justified or adjusted. Please refer to USP 24, General Information Chapter <1231>, page 2163.

If you have any questions, call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

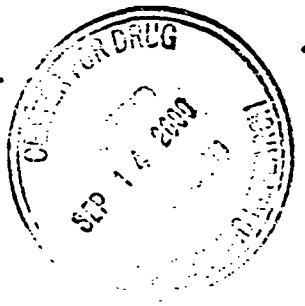
Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Confidential

September 13, 2000 ORIGINAL



Susan Allen, M.D.,
Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
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www.seronousa.com

ORIG AMENDMENT

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Information Request: Updated Package Insert

Dear Dr. Allen,

BL

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Reference is also made to correspondence from the Division on August 31, 2000 whereby edits and comments to the draft package insert were made. Reference is also made to a fax from the Division on September 12, 2000 with comments from the Biopharm Reviewer.

Herewith, please find the revised draft annotated package insert. For the convenience of the reviewers, the label is provided in both paper and electronic formats.

Please note that the following sections have been updated, as noted by highlighted gray text throughout the document:

1. **Clinical**: Lines 357- 408 (Administration section): Step-by-step instructions with pictorials have been added at the Agency's request.

2. **Biopharm**: Line 47: Text has been modified as per the recommendation of the Biopharm Reviewer.

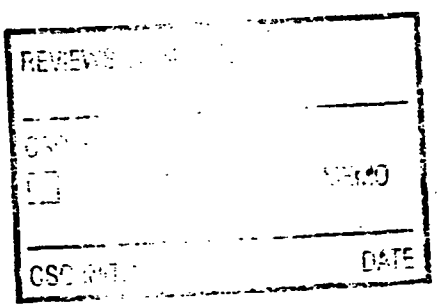
Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

Enclosure: diskette
cc: Eufrecina DeGuia (Desk Copy)



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serono

ORIGINAL

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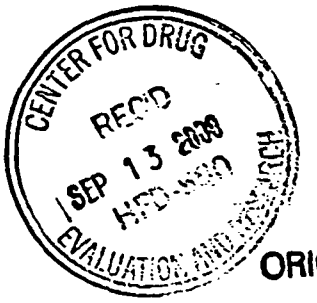
Norwell, MA 02061
Tel: 781-928-9000
Fax: 781-871-6754
www.seronousa.com

September 12, 2000



ORIG AMENDMENT

Susan Allen, M.D.,
Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Information Request: Revised Carton/Container/Diluent Labels

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to fax from the Division dated August 2, 2000 whereby comments and recommendations to the outer packaging of the Ovidrel® drug product and diluent were made (refer to Attachment 1).

Herewith, please find the revised carton/container/diluent labeling, which incorporate the comments and recommendations of the Agency in the above-referenced letter.

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

REVIEWS COMPLETED
CSO INITIALS DATE

cc: Eufrecina DeGuia (Desk Copy)

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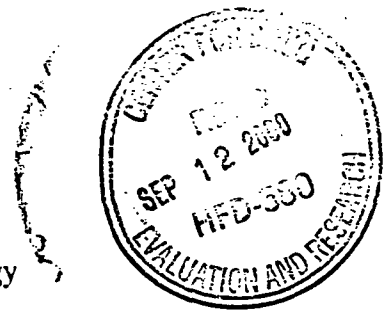
DUPLICATE



Serono, Inc.
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Norwell, MA 02061
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September 11, 2000

Susan Allen, M.D.,
Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BL

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Information Request: Updated Package Insert

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to correspondence from the Division on August 31, 2000 whereby edits and comments to the draft package insert were made.

Herewith, please find the revised draft annotated package insert. For clarity, the version with edits and comments sent by the Division is provided in Attachment 1. Additionally, for the convenience of the reviewers, the label is provided in both paper and electronic formats.

Please note that the following sections have been updated, as noted by highlighted gray text throughout the document:

Clinical Section:

1. Although Serono feels strongly that comparative data from Profasi® is necessary for prescribers to make informed decisions about the use of this product, at the Agency's request, [redacted] Efficacy and Safety Tables. Table titles have been modified to reflect r-hCG data only.

2. The word [redacted] has been replaced with 'urinary-derived hCG', or 'an approved urinary-derived hCG product', where requested.

3. Line 98: 'open-label' has been inserted after 'randomized'.

4. Line 104: The sentence beginning, '[redacted] has been deleted and replace with 'Ovidrel® 250 mcg and Ovidrel® 500 mcg were both found to be statistically equivalent to the approved urinary-derived hCG product and to each other.' Similar summary statements for Study 7648 and Study 8209 were made on Lines 122 and 138, respectively.

5. Line 149: (Indications and Usage): The underlined phrase has been added to the sentence, "Ovidrel® is indicated for the induction of final follicular maturation and early luteinization in infertile women who have undergone pituitary desensitization and who have been appropriately pretreated...".

6. Line 236: (Precautions/General): The following statement was added at the request of the Agency an modified slightly based on information provided to the Medical Reviewer: "After the exclusion of pre-existing conditions, elevations in ALT were found in 10 (3%) of 335 patients receiving Ovidrel®250 mcg, and in 16 (4.8%) of 328 patients receiving urinary-derived hCG. The elevations ranged up to 1.2 times the upper limit of normal. The clinical significance of these findings is not known."

7. Line 291: A statement on local tolerance has been added to the text.

8. Line 341: The underlined words have been inserted, "Ovidrel should be administered..."

9. Administration section: Step-by-step instructions are currently being prepared and will be submitted with or before the next label revision.

Biopharm:

10. Line 48: [redacted] has been removed from Table 1, at the Agency's request. A statement has been added to the text instead.

11. Line 49: Text has been modified, as per the Agency's request. The statement regarding gender effect, originally added at the Agency's request, was thought to have been inadvertently removed and was put back into the text.

Chemistry:

12. Line 29: The statement on the inactive ingredients, which had been inadvertently removed, has been added back into the Description section.

13. Line 372: [redacted] has been replaced by "Distributed by Serono, Inc."

serono

Please note that Serono, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

Enclosure: diskette
cc: Eufrecina DeGuia (Desk Copy)

MEMORANDUM

DATE: September 11, 2000

TO: HFD-580

FROM: Lisa A. Kammerman, Ph.D. /S/ 9/11/00
Team Leader
Division of Biometrics II (HFD-715)

SUBJECT: NDA 21-149 (Ovidrel)

The applicant, Serono, submitted two-sided 90% confidence intervals for the primary endpoints. At the request of HFD-580, they resubmitted the results as two-sided 95% confidence intervals. The medical officers found these results satisfactory.

No other statistical issues arose in the medical review of NDA 21-149.

Cc:
Orig HFD-580
HFD-580/FDe-Guia,RBennett,SSlaughter
HFD-715/ENevius/LKammerman

Minutes of Teleconference

Date: September 6, 2000 **Time:** 11:10 - 11:22 AM **Place:** Parklawn; Ms. Moore's Office

NDA: 21-149 **Drug Name:** Ovidrel (chyoriogonadotropin, alfa) 250

Indication: final follicular maturation and ovulation in women assisted reproductive technology (ART)

Type of Meeting: Labeling comments

External Constituent: Serono Laboratories, Inc.

FDA Lead: Ms. Diane Moore **External Participant Lead:** Ms. Debbie DeMuria

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Participant:
Debbie DeMuria, Pharm. D. - Senior Regulatory Associate, Serono Laboratories

Meeting Objective: To convey labeling comments from the Medical Officer.

Background: Referenced labeling dated August 14, 2000.

Discussion Items:
- the establishment inspection for the site was canceled on August 14, 2000; the sponsor is asking whether an official letter would be forthcoming notifying the plant of the cancellation

Decisions:
- the term should be replaced globally throughout the labeling with "an approved urinary-derived hCG product" (see **Clinical Studies** section, **Assisted Reproductive Technologies (ART)** subsection, first paragraph, first sentence) (line 109)
- in the **Clinical Studies** section, **Assisted Reproductive Technologies (ART)** subsection, first paragraph, first sentence that begins, "The safety and efficacy . . ." the phrase, "open-label" should be inserted after the word "randomized" so the sentence reads "The safety and efficacy of Ovidrel® 250 mcg and Ovidrel® 500 mcg administered subcutaneously versus an approved urinary-derived hCG product 10,000 USP U administered intramuscularly were assessed in a randomized, open-label, multi-center study in infertile women undergoing *in vitro* fertilization and embryo transfer (Study 7972)." (line 110)
- the second paragraph, third sentence that begins, " " should be replaced by the following sentence: "Ovidrel® 250 mcg and Ovidrel® 500 mcg were both found to be statistically equivalent to the approved urinary-derived hCG product and to each other." (line 115)

- in the fourth paragraph, first sentence that begins, "The safety and efficacy . . ." the term "*in vitro*" should be italicized and ——— should be deleted and the phrase "of an approved urinary-derived hCG product" should be inserted after "IU" so that the sentence reads, "The safety and efficacy of Ovidrel® 250 mcg administered subcutaneously versus 5,000 IU of an approved urinary-derived hCG product administered subcutaneously were assessed in a second, randomized, multi-center study in infertile women undergoing *in vitro* fertilization and embryo transfer (Study 7648)." (line 125)
- in the **Clinical Studies** section, **Ovulation Induction (OI)** subsection, the first paragraph, first sentence that begins, "The safety and efficacy . . ." the term ——— should be deleted and the phrase "of an approved urinary-derived hCG product" should be inserted after the term "5,000 IU" so the sentence reads "The safety and efficacy of Ovidrel® 250 mcg administered subcutaneously versus 5,000 IU of an approved urinary-derived hCG product administered intramuscularly were assessed in a double-blind, randomized, multi-center study in anovulatory infertile women (Study 8209) which was conducted in 19 centers in Australia, Canada, Europe and Israel." (line 141 and 142)
- in the **INDICATION AND USAGE** section, first paragraph, first sentence that begins, "Ovidrel® (choriogonadotropin alfa for injection) . . ." the phrase, "undergone pituitary desensitization and who have" should be inserted after the word "have" so that the sentence reads "Ovidrel® (choriogonadotropin alfa for injection) is indicated for the induction of final follicular maturation and early luteinization in infertile women who have undergone pituitary desensitization and who have been appropriately pretreated with follicle stimulating hormones as part of an Assisted Reproductive Technology (ART) program such as *in vitro* fertilization and embryo transfer."
- in the **PRECAUTIONS** section, **General** subsection, the following sentence should be added: "After the exclusion of pre-existing conditions, elevations in ALT were found —— of patients receiving Ovidrel®. The elevations ranged up to 1.2 times the upper limit of normal. The clinical significance of these findings is not known."
- in the **DOSAGE AND ADMINISTRATION** section, **For Subcutaneous Use Only** subsection, first paragraph, first sentence that begins, "Ovidrel® 250 mcg one day . . " the phrase "should be administered" should be inserted after the term "250 mcg" so that the sentence reads, "Ovidrel® 250 mcg should be administered one day following the last dose of the follicle stimulating agent."
- in the **DOSAGE AND ADMINISTRATION** section, Administration: subsection, step-by-step instructions with pictorials or diagrams should be added
- revised labeling should be submitted by COB September 11, 2000

Action items

	Item :	**Responsible Person :**	**Due Date:**
•	submit revised labeling	Serono	September 11, 2000
•	check on status of inspection with Chemists	Ms. Moore	September 9, 2000
•	submit meeting minutes	Ms. Moore	October 6, 2000

/S/ 9/11/00
signature, recorder

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
HFD-580
HFD-580/MMann/SSlaughter/RBennett/SUAllen/EDeGuia

Concurrences: TRumble 9.7.00
final: September 11, 2000
filename: N21149TC9600.doc

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September 6, 2000

ORIGINAL

Susan Allen, M.D.,
Director
Division of Reproductive and Urologic
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
13C

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Amendment to Pending Application: Withdrawal of Alternate Packaging Facility

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to an Agency request made on August 31, 2000 for withdrawal of the alternate packaging facility at [redacted] from the pending NDA file (Volume 11, page 195).

Accordingly, we hereby withdraw the alternate packaging facility from the above referenced NDA.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at (781) 681-2267, or the undersigned at (781) 681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

REVIEWS COMPLETED
OSO ACTION:
☐ LETTER ☐ E-MAIL ☐ MEMO
OSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 07 2000
HFD-580

serono

Serono, Inc. 100 Longwater Circle, Norwell, MA 02061

FAX

Date: September 5, 2000

Number of pages including cover sheet: 3

To: Ms. Diane Moore for:
Ms. Freshnie DeGuia
DRUDP (HFD-580)

Phone: (301) 827 - 5424
Fax: (301) 827 - 4267

RE: Ovidrel NDA 21-149: Response for Medical Officer (Dr. R. Bennett)

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 – 2267
Fax: (781) 878 – 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Diane,

This fax provides a response to the Medical Reviewer's question regarding a discrepancy between Table 3 of the Ovidrel® Package Insert and Table 26 (page 97) of the 7927 Study Report.

For clarification, Table 26 of the 7927 Study Report is about 'pregnancy outcomes' while Table 3 of the Ovidrel package insert is about 'patients'.

Table 26 (7927 Report)

Based on the Pregnancy Outcome Report for the 7927 study, below are 5 different pregnancy outcomes:

1. Pre-clinical spontaneous abortion
2. Ectopic pregnancy
3. Spontaneous abortion
4. Other pregnancy, and
5. Live birth

If a patient had a "pre-clinical spontaneous abortion" (as shown in the above #1 category), she was considered to be "biochemically pregnant". Any patient who had any outcome other than "pre-clinical spontaneous abortion" (i.e., categories #2 through 5) was considered to be "clinically pregnant".

A "clinically pregnant patient" might have multiple clinical pregnancy outcomes.

Table 26 shows that of the 94 patients treated with Ovidrel 250 mcg, 37 had a positive pregnancy test and 33 were confirmed pregnant by ultrasound. There were 4 biochemical pregnancies (ie. (+) preg test but no confirmation of a gestational sac). Biochemical pregnancies are not categorized as "clinical pregnancies not reaching term" since they were never determined to be "clinical" pregnancies.

Among the 33 clinically pregnant women, there were a total of 42 pregnancy outcomes. Twenty four women had just one outcome reported, while 9 patients had two outcomes reported. How can one pregnant patient produce two pregnancy outcomes?

Examples:

- 'Live birth' and 'spontaneous abortion' may occur in the same patient if initially more than one fetal sac was seen on ultrasound, but later one or more sacs are lost and spontaneously aborted.
- 'Live birth' and 'other' outcome may occur if a patient elects to terminate one or more of the fetuses, so called "selective abortion", or when a fetal sac disappears in the absence of any medical event (no bleeding or visible loss of fetal tissue).

Table 3 (Package Insert)

Table 3 in the label is correct. There were a total of 4 clinically pregnant patients who did not reach term. There were 29 patients who did have a live birth. Of the 29 who had a live birth, there were 9 patients who in addition to delivering a baby, had another outcome - either spontaneous abortion or "other" outcome.

For your reference, a summary of the patient data listing is provided. Please note there are only 4 patients who had clinically pregnancies but did not give a live birth. As shown in the table below, they were Patient # 010009, 030008, 050004 and 090016. In addition, as shown in the last row of the table, among these 33 clinically pregnant patients, they were 1 ectopic pregnancy, 7 spontaneous abortions and 5 "other" pregnancies. For reference in the NDA, please refer to the derived data listing (the very last listing in the Statistical Appendix 16.1.9, (Volume 61, section 3.38, page 412 in the NDA).

We sincerely apologize for any confusion regarding the above tables. Please call me if I can be of further assistance at 781 – 681 – 2261.

Sincerely,

Debbie DeMuria

Patient No	Ectopic Pregnancy	Spontaneous Abortion	Other pregnancies	Live Birth	Clinically Pregnant Patient	Clinically pregnancies not reaching term
010002				Yes	Yes	
010009	Yes			No	Yes	Yes
010017				Yes	Yes	
010024				Yes	Yes	
020004				Yes	Yes	
020007				Yes	Yes	
020014				Yes	Yes	
030003				Yes	Yes	
030005				Yes	Yes	
030008		Yes		No	Yes	Yes
040003		Yes		Yes	Yes	
040010				Yes	Yes	
050003				Yes	Yes	
050004			Yes	No	Yes	Yes
050016				Yes	Yes	
050020			Yes	Yes	Yes	
070006		Yes		Yes	Yes	
080008		Yes		Yes	Yes	
080015				Yes	Yes	
090005				Yes	Yes	
090013		Yes		Yes	Yes	
090016		Yes		No	Yes	Yes
090017				Yes	Yes	
100001				Yes	Yes	
120005				Yes	Yes	
150008				Yes	Yes	
160004				Yes	Yes	
170006			Yes	Yes	Yes	
170010			Yes	Yes	Yes	
190005		Yes		Yes	Yes	
190009			Yes	Yes	Yes	
200003				Yes	Yes	
200005				Yes	Yes	
Total # of "Yes"	1	7	5	29	33	4

serono

Serono, Inc. 100 Longwater Circle, Norwell, MA 02061

FAX

Date: 31 August, 2000

Number of pages including cover sheet: 2

To: Ms. Freshnie DeGuia
DRUDP (HFD-580)

Phone: (301) 827 - 5424
Fax: (301) 827 - 4267
RE: Ovidrel NDA 21-149

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267
Fax: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

This fax provides a response to the Medical Reviewer's question regarding ALT levels in Study 7927.

Question:

In the 7927 Study Report (Table 35), 26 patients are listed as having normal ALT levels at baseline to high levels after treatment. 3 patients are listed as high at baseline and remaining high after treatment. Please provide the individual data listings for these 29 patients.

Please see the attached data listings, which were derived from the Clinical Laboratory Data Listings in Appendix 16.1.9 (Section 3.20, Volume 61, page 112)"

As shown in the listing, there were 26 patients who shifted to abnormal high from a normal status at baseline. Of these 26 patients, 6 patients were in the Ovidrel® 250 mcg group, 9 patients were in the Ovidrel® 500 mcg group and 11 patients were in the Profasi® group. Three (3) additional patients who remained at a abnormal high status were all from the 250 Ovidrel® 250 mcg group.

Please call me at 781 – 681 – 2267 should you have any further questions. Sincerely, Debbie

Listing in Support of Clinical Laboratory Data : ALT (IU/L) Abnormality*

Treatment Group	Patient No.	Baseline Value	Baseline Status	Last Visit Value	Last Visit Status
250 ug r-hCG	010002	20.0	Normal	47.0	High
	010009	29.0	Normal	39.0	High
	010012	18.0	Normal	41.0	High
	090017	16.0	Normal	38.0	High
	130001	25.0	Normal	36.0	High
	140007	37.0	High	70.0	High
	150005	61.0	High	48.0	High
	160006	77.0	High	48.0	High
	200005	13.0	Normal	43.0	High
500 ug r-hCG	010013	19.0	Normal	39.0	High
	050001	12.0	Normal	53.0	High
	050014	33.0	Normal	45.0	High
	050015	16.0	Normal	47.0	High
	070005	14.0	Normal	42.0	High
	090009	13.0	Normal	36.0	High
	120003	12.0	Normal	40.0	High
	130006	17.0	Normal	44.0	High
	150007	16.0	Normal	93.0	High
Profasi®	010003	20.0	Normal	35.0	High
	020001	18.0	Normal	51.0	High
	050009	27.0	Normal	86.0	High
	100015	19.0	Normal	43.0	High
	120004	15.0	Normal	45.0	High
	120007	19.0	Normal	76.0	High
	130002	25.0	Normal	63.0	High
	130012	24.0	Normal	36.0	High
	140018	16.0	Normal	150.0	High
	170016	22.0	Normal	42.0	High
	180008	28.0	Normal	36.0	High

*Include patients who shifted to a abnormal high status from normal at baseline (26) or remained at abnormal high status (3).

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August 31, 2000

ORIGINAL

Susan Allen, M.D.
Director,
Division of Reproductive and Urologic Drug
Products, HFD-580 (Room 17-B-45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
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HFD

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Response to Request for Information: Biopharm

Dear Dr. Allen:

Reference is made to NDA 21-149 for Ovidrel® (choriogonadotropin alfa for injection) submitted on November 23, 1999. Further reference is made to a teleconference on July 27, 2000 with the Biopharm Reviewer where Serono confirmed that the formulation of the to-be marketed Ovidrel® drug product is the same as that studied in clinical trials. Reference is also made to an additional request from the Biopharm Reviewer on August 28, 2000 for Serono to provide a written statement of the above confirmation in terms of composition, site of manufacture and manufacturing procedures.

Accordingly, Serono confirms that the formulation of Ovidrel® intended for market is identical in composition to that used in clinical trials. (Please refer to NDA 21-149, Volume 11, page 391). The commercial manufacturing process developed at our pilot manufacturing facility in ——— was successfully transferred to our commercial manufacturing facility in ——— without modification.

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns regarding this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate at (781) 681-2267 or the undersigned at (781) 681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President, Regulatory Affairs

REVIEWS COMPLETED

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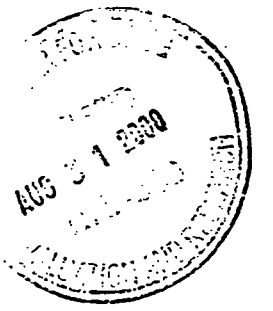
August 29, 2000

ORIGIN



Susan Allen, M.D.
Director, Division of Reproductive and Urologic
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 21-149
Ovidrel® (choriogonadotropin alfa)
Response to Request for Information: CMC

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to an August 7, 2000 submission containing responses to FDA's request for additional information and to an August 25, 2000 teleconference with the Chemistry Reviewer.

As discussed in the above-cited teleconference, please find enclosed herewith the following information:

Attachment 1 — a revised Drug Substance Specifications table which includes the [redacted] testing

Attachment 2 — a letter from [redacted] authorizing the Agency to cross-reference [redacted] for the stoppers

Please note that Serono, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate, at (781) 681 2267 or the undersigned at (781) 681 2298.

Yours Sincerely,

Robert M. Kuster for P.W.J.

Pamela Williamson Joyce
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 29 2000

Dear Dr. [redacted]

Between May 1 and May 9, 2000, Ms. Brunilda Torres, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #GF7927) of the investigational drug, Ovidrel® (recombinant human chorionic gonadotropin) performed for Serono Laboratories, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Torres presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to conduct your study in accordance with the approved protocol.

   A. Treatment of subject [redacted] was initiated prior to receipt of hormone analyses which indicated an elevated FSH level meeting exclusion criteria.

   B. Semen analyses of the partners of subjects [redacted] were obtained more than six months prior to their enrollment; therefore these subjects should have been excluded from the study.

2. You failed to maintain adequate and accurate records.

   The majority of the original laboratory testing records (print-outs) for hCG and estradiol were destroyed after two years. Please note that Federal regulations require that records must be maintained for two years following the date of approval of a marketing application or for two years after an Investigational New Drug Application is discontinued and the FDA has been notified.

Because of the nature of the violations of FDA regulations discussed above, we request that you inform this office, in writing, of the actions you have taken or plan to take to address these observations and to bring your procedures into compliance with FDA regulations.

We appreciate the cooperation shown Investigator Torres during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm. NDA 21-149
HFD-580/Best
HFD-580/Willett
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File #010114
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-SE250/Chappell
HFR-SE2585/Torres

CFN #
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI no response required
__x__3)VAI-R response requested
_____4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____5)OAI-WL warning letter
_____6)OAI-NIDPOE

The inspection is classified VAI-R because the investigator's approach appears to be somewhat casual with respect to subject enrollment, and the timing of the destruction of the majority of the laboratory records is not in conformity with FDA regulations. A response is therefore requested from the investigator that will outline how these deficiencies will be corrected or avoided in future studies.

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
__x__deviation from protocol
__x__inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

E:/blay. [redacted]
drafted/rab/8.14.00
reviewed:/
final:mgk 8/25/00

Note to Review Division and DSI Recommendation:

The field investigator reviewed and compared the source documents against respective case report forms and tabulated data for 8 of the 24 subjects enrolled into protocol #GF7927 at Dr. [redacted] site and reviewed portions of additional study records. The data appear acceptable for use in support of drug claims.

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SERONO GROUP

Confidential

Serono
PART OF THE ARES-SERONO GROUP

SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

August 28, 2000

ORIGINAL

Susan Allen, M.D., Director,
Division of Reproductive and Urologic
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BC

NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
General Correspondence: CMC – Response to Request for Revised Bioidentity Specification

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a teleconference on August 17, 2000 between Dr. D-G Wu, Dr. Y. Yang and Serono whereby a request was made to revise the proposed bioidentity specification for consistency with the proposed bioassay specification.

Accordingly, Serono commits to implement a specification for bioidentity of _____ in the stability protocol for all future timepoints of the ongoing and post-approval studies.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate, at (781) 681 2267 or the undersigned at (781) 681 2298.

Yours Sincerely,

for P.W.J.

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

rono Laboratories, Inc. 100 Longwater Circle Norwell, MA 02061

FAX - ORIGINAL

Date: 28 August 2000

Number of pages including cover sheet: 4

CONFIDENTIAL

To: Eufrecina DeGuia
Project Manager, DRUDP
CDER, FDA

re: Ovidrel NDA 21-149

Phone: (301) 827 5424
Fax phone: (301) 827 4267

From: Lisa S. Mills
Regulatory Affairs

Phone: (781) 681-2273
Fax phone: (781) 878-5001

REMARKS: ☐ Urgent ☐ For your review ☐ Reply ASAP ☐ Please comment

ar Ms. DeGuia,

ase find attached the information you requested from Debbie DeMuria on August 21, 2000.

ope this meets your needs.

icerely,

a S. Mills
nager, Regulatory Affairs

ORIG AMENDMENT

BS

AUG 2 9 2000

RECEIVED

Ovidrel

(choriogonadotropin alfa)

NDA 21-149

Response to FDA Request for Information

Serono, Inc.
100 Longwater Circle
Norwell, MA 02061
Telephone (781) 982-9000
FAX (781) 878-5001

Date: August 2000

1. Request #1

For Study 7927, please provide a statistical comparison between Ovidrel 250 mcg and Profasi 10,000 USP Units for both primary and secondary endpoints.

The statistical comparison for the primary endpoint and secondary endpoints between Ovidrel 250 mcg and Profasi 10,000 USP Units in Study 7927 (IVF/ET) is provided in the table below:

Endpoint	Parameter	Ovidrel® 250 mcg (n = 94)	Profasi® 10,000 USP Units (n = 92)	p-value
Primary	Mean number of oocytes retrieved per patient	13.60	13.66	0.954(a)
Secondary	Mean number of mature oocytes retrieved per patient	7.6	9.7	0.210(a)
Secondary	Mean number of 2 PN fertilized oocytes per patient	7.2	7.8	0.187(b)
Secondary	Mean number of 2 PN or cleaved embryos per patient	7.6	8.2	0.160(b)
Secondary	Implantation rate per embryo transferred (%)	18.7	17.3	0.862(b)
Secondary	Mean mid-luteal serum progesterone levels (nmol/L*)	423	469	0.136(b)
Secondary	Clinical pregnancy rate per initiated treatment cycle (%)[T]	35.1	35.9	> 0.999(c)
Secondary	Clinical pregnancy rate per transfer (%)[T]	36.3	37.1	> 0.999(c)

[T]Clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heartbeat activity) was detected by ultrasound on day 35-42 after hCG administration)

*nmol/L ÷ 3.18 = ng/mL

(a) p-value: two-way ANOVA on raw data
(b) p-value: two-way ANOVA on ranked data
(c) p-value: two-sided Fisher's exact test

2. Request #2

For the pivotal trials (2 IVF/ET, 1 OI), please recalculate the data between Ovidrel 250 mcg and Profasi at the 95% Confidence Interval (2-sided test).

The 95% confidence intervals (CI) of the treatment difference in the primary efficacy endpoint between the 250 mcg Ovidrel and the Profasi groups for Studies 7927, 7648 and 8209 are presented below. Please note the results are based on the intent-to-treat patients.

Study	Parameter (Primary Efficacy Endpoint)	95% Confidence Interval (2-sided test)
7927 (IVF)	Number of Oocytes Retrieved per Patient	(-2.123, 2.003)
7648 (IVF)	Number of Oocytes Retrieved per Patient	(-1.437, 1.414)
8209 (OI)	Ovulation Rate	(-3.4%, 19.1%)

DEPARTMENT OF HEALTH & HUMAN SERVICES

DeGuia

Doc. Rm

Food and Drug Administration
Rockville MD 20857

Dear Dr. [redacted]

Between June 26 and June 30, 2000, Ms. Brunilda Torres and Dr. Roy Blay representing the U. S. Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol #GF7648) of the investigational drug Ovidrel® (recombinant human chorionic gonadotropin). You performed this study for Serono Laboratories. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

At the conclusion of the inspection, Ms. Torres and Dr. Blay met with you to discuss the items listed on the Form FDA 483, Inspectional Observations. We have reviewed the inspection report.

We understand that your study was not conducted under a U.S. Investigational Drug Application (IND). For your future reference, however, we offer our comments in the same manner as we would if the study had been performed under a U.S. IND. Our findings are summarized below:

1. You did not adhere to the study protocol.

   a. Subject #030001 did not receive rhCG within the 24-hour period following the last administration of Gonal-F® and nafarelin.

   b. Subject #030006 did not have a blood sample collected on the day of oocyte pick-up for hormone level determination by the central laboratory.

   c. Subject #030018 did not have local estradiol measurements done either on the day of rhCG administration or on the day of oocyte pickup. In addition, a pregnancy test was not done prior to initiating study treatment.

2. You did not promptly report a serious adverse event to the sponsor.

   Subject #030025 experienced ovarian hyperstimulation syndrome (OHSS) which resulted in hospitalization from [redacted] This event was not reported to the sponsor until [redacted] instead of within 24 hours of its occurrence as required by protocol.

3. You did not maintain adequate and accurate records.

   Subject #0300020 noted episodes of dry mouth, burning eyes, sweating, and tiredness in her patient diary that were not recorded on the Case Report Form.

We appreciate the cooperation shown Ms. Torres and Dr. Blay during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/ [redacted]

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm. NDA 21-149
HFD-580/Review Div. Dir.
HFD-580/DeGuia
HFD-580/Bennett
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File # 010172
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-SE250/Chappell
HFR-SE250/Torres

CFN: #

Field Classification: VAI

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_____1)NAI
__x__2)VAI no response required
_____3)VAI-R response requested
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_____5)OAI-WL warning letter
_____6)OAI-NIDPOE

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
__x__deviation from protocol
__x__inadequate records
__x__failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

drafted/rab/8.23.00
reviewed:/
final:mgk 8/25/00

Note to Review Division and DSI Recommendation:
The field investigators compared the source documentation with the Case Report Files and the data listings provided by the sponsor for 15 of the 33 subjects receiving hCG in protocol #GF7648 at Dr. [redacted] site. The data appear acceptable for use in support of drug claims.

Meeting Minutes

Date: August 21, 2000 **Time:** 11:00 AM – 12:00 PM **Location:** PKLN; 17B-43

NDA: 21-149 **Drug Name:** Ovidrel (choriogonadotropin alfa for injection)

Indication: final follicular maturation and ovulation in women undergoing ovulation induction and oocyte maturation prior to fertilization in women undergoing Assisted Reproductive Technology (ART)

Type of Meeting: Status/Labeling Meeting (9-month)

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Susan Allen, M.D., M.P.H. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. - Team Leader, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Duu Gong Wu, Ph.D. - Chemistry Team Leader, Division of Metabolic and Endocrine Drug Products DMEDP, (HFD-510)
Yvonne Yang, Ph.D. - Chemistry Reviewer, DMEDP, (HFD-510)
Karen Davis-Bruno, Ph.D. – Pharmacologist, DRUDP (HFD-580)
Eufrecina DeGuia - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objectives: To discuss the status of the Team's reviews and to get the appropriate revisions of the label from all disciplines.

Background: This application is on a 10-month PDUFA review clock and the User Fee goal date is September 24, 2000. It was determined at the previous status meeting that there are some minor Chemistry deficiencies; an Information Request letter (IR) letter was sent to the sponsor on July 31, 2000 outlining the deficiencies. Serono sent a letter sent to the Division addressing those deficiencies on August 7, 2000.

Decisions reached:
Clinical:

- sponsor needs to re-analyze data from all the studies using a 2-sided 95% Confidence Interval (CI); or a 1-sided 97.5% CI, as appropriate; the Ovulation Induction study was done on 95% 1-sided CI
- the primary efficacy analysis for Study 7927 should include a direct comparison for clinical and statistical significance between the 250 mcg Ovidrel dose and the 10,000 IU Profasi dose and this should be submitted to the Agency
-

- [redacted]

- comments regarding labeling:
  - [redacted] should be deleted
  - under **WARNINGS** section
    - under **Overstimulation of the Ovary Following hCG Therapy**: "Ovarian Enlargement" and "Ovarian Hyperstimulation Syndrome (OHSS)" at the beginning of the paragraphs should be bolded or underlined and single-spaced from the paragraphs
    - under **Multiple Births**: in the sentence that begins with "Multiple births…", "[redacted] live deliveries [redacted] should be changed to "17 of 55 live deliveries (30.9%)"
  - under **ADVERSE REACTIONS** section: the number of patients receiving Ovidrel should be changed from 325 to 335

Chemistry
- secondary review is being finalized
- sponsor has provided all the information the Division requested in the Information Request (IR) letter sent on July 31, 2000
- Labeling comments in the **DESCRIPTION** Section:
  - the two sentences that start with [redacted] " should be deleted
  - label need to contain the same information about the active and inactive ingredients/vial (not the final concentration or deliverable amount); "30 mg Sucrose, 0.98 mg Phosphoric acid and Sodium Chloride (for pH adjustment)" should be inserted between "choriogonadotropin alfa" and "when" in the sentence that starts with "Each vial contains…"

Clinical Pharmacology and Biopharmaceutics
- the secondary review is being finalized
- comments regarding labeling:
  - in the **CLINICAL PHARMACOLOGY** section:
    - under **Pharmacokinetics** subsection: the statement that states "[redacted] should be deleted; data that pertain to [redacted] should be deleted from Table 1; the word [redacted] should be deleted from the last sentence
    - under **Distribution**: the phrase "appears to be" should be changed to "is" and the last sentence should be deleted
    - under **Metabolism and Excretion**: the statement that states "After intravenous administration of 250 mcg to healthy down regulated females, the mean terminal half-life of 26.5 ± 2.5 hours and the total body clearance is 0.29 ± 0.04 L/h." should be inserted between the first sentence and the last sentence
    - under **Pharmacodynamics**: the phrase in [redacted] should be deleted
    - under **Population pharmacokinetics and pharmacodynamic**: the paragraph should read " In patients undergoing in-vitro fertilization/embryo transfer given Ovidrel® subcutaneously to trigger ovulation, the results of a population PK/PD analysis generally supported the data obtained in healthy subjects. Pharmacokinetic parameters for Ovidrel® include mean elimination half-life of 29.2 hours, median apparent clearance of 0.51 L/hr and median apparent volume of distribution of 21.4 L."

Pharmacology/Toxicology
- the sponsor has incorporated the proposed changes into the draft labeling

Microbiology
- expected date of completion of the review will be late August

Action Items:
- request the sponsor to re-analyze data from all the studies using 95% two-sided Confidence Interval (CI)
- request the sponsor to do a direct comparison between 250 mcg Ovidrel and 10, 000 IU Profasi

9/18/00
Signature, minutes preparer

/S/
Concurrence, Chair

9/18/00

drafted: EDeGuia/08.22.00

cc:
NDA Arch:
HFD-580 Div. File
HFD-580/DEGuia
HFD- 580/SAllen/MMann/DShames/SSlaughter/LKammerman/TRumble/
AParekh/KDavis-Bruno/RBennett/MRhee/
HFD-510-DWu/YYang
Concurrences:
TRumble,MRhee,KDavisBruno08.28.00/DWu08.29.00/RBennett09.08.00/SSlaughter09.15.00/
RKavanagh09.18.00
Final: EDeGuia09.18.00

Meeting Minutes

ORIGINAL

serono

serono, Inc. — 100 Longwater Circle, Norwell, MA 02061

FAX

ORIG AMENDMENT

DM

Date: 18 August, 2000

Number of pages including cover sheet: 3

To: Ms. Freshnie DeGuia
DRUDP (HFD-580)

Phone: (301) 827 - 5424
Fax: (301) 827 - 4267

RE: Ovidrel NDA 21-149

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 – 2267
Fax: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

This fax is in response to the Medical Reviewer's request for information regarding reference to Table 8 of the Ovidrel Package Insert, which has been modified to _____ The attached table includes all AE's (regardless whether >2% or ≤ 2%) by body system and preferred term for the Ovidrel 250 mcg group across 3 ART studies (using the WHOART coding dictionary). This table will essentially provide the information for the validation of Table 8 as well as the text specified in Lines 289 - 297 of the package insert.

Unfortunately, the data is found in multiple locations throughout the NDA for the following reasons:

- Table 6 in the 120 day safety update report – it was presented at the "body system" level only (not preferred term); and it included the Ovidrel 500 mcg group.
- Study Report 7927 (Table 28) and Study Report 7648 (Table 32) – single reports only.
- Study Report 9073 (Table 25) – the AE's were coded using the COSTART dictionary. In order to combine this study with two other ART studies (i.e., 7648 and 7927), the AE's for the 9073 study were re-coded by using the WHOART dictionary accordingly.

Please call if I can be of further assistance: 781 – 681 – 2267 Sincerely, debbie

REVIEWS COMPLETED

ACTION

☐ LETTER ☐ FAX ☐ MEMO

DATE

Table 8
Percent of Patient with Adverse Events Following hCG Administration by Body System, Preferred Term and Treatment Group, ART Studies 7927, 7648 and 9073

Body System / Preferred Term	hCG-Treated Patients	
	Ovidrel (n=236)	Profasi® (n=229)
	Incidence Rate * % (n)	Incidence Rate * % (n)
At Least One Adverse Event	33.1% (78)	42.4% (97)
APPLICATION SITE DISORDERS	14.0% (33)	25.3% (58)
INJECTION SITE PAIN	7.6% (18)	15.7% (36)
INJECTION SITE INFLAMMATION	1.7% (4)	8.3% (19)
INJECTION SITE BRUISING	4.7% (11)	3.9% (9)
INJECTION SITE REACTION	1.3% (3)	3.5% (8)
GASTRO-INTESTINAL SYSTEM DISORDERS	8.5% (20)	8.3% (19)
ABDOMINAL PAIN	4.2% (10)	3.5% (8)
NAUSEA	3.4% (8)	3.9% (9)
VOMITING	2.5% (6)	2.2% (5)
FLATULENCE	0.8% (2)	1.3% (3)
DIARRHOEA	0.8% (2)	0.9% (2)
APPENDICITIS	(0)	0.4% (1)
CONSTIPATION	(0)	0.4% (1)
DYSPEPSIA	(0)	0.4% (1)
HAEMORRHOIDS	(0)	0.4% (1)
HICCUP	0.4% (1)	(0)
REPRODUCTIVE DISORDERS, FEMALE	5.5% (13)	5.2% (12)
OVARIAN HYPERSTIMULATION	1.7% (4)	1.7% (4)
INTERMENSTRUAL BLEEDING	0.8% (2)	1.7% (4)
BREAST PAIN FEMALE	0.4% (1)	0.9% (2)
PREGNANCY ECTOPIC	0.4% (1)	0.9% (2)
VAGINAL HAEMORRHAGE	0.4% (1)	0.4% (1)
CERVIX LESION	0.4% (1)	(0)
LEUKORRHOEA	0.4% (1)	(0)
UTERINE DISORDER NOS	0.4% (1)	(0)
VAGINAL DISCOMFORT	0.4% (1)	(0)
VAGINITIS	0.4% (1)	(0)
SECONDARY TERMS (POST-OPERATIVE PAIN)	4.7% (11)	3.9% (9)
POST-OPERATIVE PAIN	4.7% (11)	3.9% (9)
BODY AS A WHOLE - GENERAL DISORDERS	3.0% (7)	3.9% (9)
PAIN	1.7% (4)	1.7% (4)
FEVER	0.8% (2)	0.4% (1)
ABDOMEN ENLARGED	(0)	0.9% (2)
BACK PAIN	0.4% (1)	0.4% (1)
HOT FLUSHES	0.4% (1)	(0)
MALAISE	0.4% (1)	(0)
PALLOR	(0)	0.4% (1)
CENTR & PERIPH NERVOUS SYSTEM DISORDERS	2.5% (6)	2.6% (6)
DIZZINESS	0.8% (2)	1.7% (4)
HEADACHE	1.3% (3)	0.4% (1)

Table 8
Percent of Patient with Adverse Events Following hCG Administration by Body System, Preferred Term and Treatment Group, ART Studies 7927, 7648 and 9073

Body System / Preferred Term	hCG-Treated Patients	
	Ovidrel (n=236)	Profasi® (n=229)
	Incidence Rate * % (n)	Incidence Rate * % (n)
MIGRAINE	(0)	0.4% (1)
PARAESTHESIA	0.4% (1)	(0)
SKIN AND APPENDAGES DISORDERS	1.3% (3)	2.2% (5)
RASH	1.3% (3)	0.4% (1)
PRURITUS	(0)	0.9% (2)
SKIN COLD CLAMMY	(0)	0.4% (1)
SKIN DISORDER	(0)	0.4% (1)
RESPIRATORY SYSTEM DISORDERS	1.7% (4)	0.9% (2)
UPPER RESP TRACT INFECTION	0.8% (2)	0.4% (1)
RHINITIS	0.4% (1)	0.4% (1)
BRONCHITIS	(0)	0.4% (1)
COUGHING	0.4% (1)	(0)
URINARY SYSTEM DISORDERS	2.5% (6)	(0)
DYSURIA	0.8% (2)	(0)
URINARY TRACT INFECTION	0.8% (2)	(0)
ALBUMINURIA	0.4% (1)	(0)
URINARY INCONTINENCE	0.4% (1)	(0)
RESISTANCE MECHANISM DISORDERS	1.7% (4)	0.4% (1)
MONILIASIS GENITAL	0.4% (1)	0.4% (1)
ABSCESS	0.4% (1)	(0)
HERPES SIMPLEX	0.4% (1)	(0)
INFECTION FUNGAL	0.4% (1)	(0)
PSYCHIATRIC DISORDERS	1.3% (3)	0.4% (1)
INSOMNIA	0.8% (2)	(0)
EMOTIONAL LABILITY	0.4% (1)	(0)
NERVOUSNESS	(0)	0.4% (1)
HEART RATE AND RHYTHM DISORDERS	0.4% (1)	0.9% (2)
ARRHYTHMIA	0.4% (1)	0.4% (1)
PALPITATION	(0)	0.4% (1)
CARDIOVASCULAR DISORDERS, GENERAL	0.4% (1)	(0)
HEART MURMUR	0.4% (1)	(0)
LIVER AND BILIARY SYSTEM DISORDERS	(0)	0.4% (1)
HEPATIC ENZYMES INCREASED	(0)	0.4% (1)
NEOPLASM	0.4% (1)	(0)
CERVIX CARCINOMA	0.4% (1)	(0)
VISION DISORDERS	(0)	0.4% (1)
CONJUNCTIVITIS	(0)	0.4% (1)
WHITE CELL AND RES DISORDERS	0.4% (1)	(0)
LEUKOCYTOSIS	0.4% (1)	(0)

T:\BIOME\OVIDREL\GF9073\FINAL\PROGRAMS\TABLES\T_T01B.SAS 03AUG2000

*The denominator of percentage 236 for Ovidrel patients and 229 for Profasi Patients

DEPARTMENT OF HEALTH & HUMAN SERVICES

~~AFSF~~ Delaware
DCC. Rm.

Food and Drug Administration
Rockville MD 20857

AUG 17 2000

[redacted]

Dear Dr. [redacted]

Between April 24 and April 27, 2000, Ms. Janice King, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #7927) of the investigational drug, Ovidrel® (recombinant human chorionic gonadotropin) performed for Serono Laboratories, Inc. We learned from Ms. King that Dr. [redacted] is no longer with [redacted] and that you have assumed the responsibilities of the principle investigator. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator King during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm. NDA 21-[illegible]49
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HFR-SE150/Todd
HFR-S1505/King

CFN #

Field Classification: NAI

Headquarters Classification:

__X__ 1)NAI
_____ 2)VAI no response required
_____ 3)VAI-R response requested
_____ 4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____ 5)OAI-WL warning letter
_____ 6)OAI-NIDPOE

[redacted]
drafted/rab/8.11.00
reviewed:/
final:mgk 8/15/00

Note to Review Division and DSI Recommendation:

The field investigator reviewed the study-related records for four of the 21 subjects enrolled into protocol #7927 at Dr. [redacted] site and reviewed portions of additional study records. The data appear acceptable for use in support of drug claims.

FAX ORIGINAL

CONFIDENTIAL

Serono

PART OF THE ARES SERONO GROUP

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

ORIG AMEND

BM

Date: 17 August 2000

1

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149
Phone: (301) 827-4260
Fax phone: (301) 827-4267
RE: Ovidrel Clinical SAE Request

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267
Fax phone: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

Further to the information provided on patient 4-03 (Study 7648), the Study Investigator called Serono back to provide the following information:

The Investigator confirmed again that no autopsy of the baby was performed. He explained that the umbilical cord was 'too long' and strangled the baby. They tried for several days to reanimate the baby, but unfortunately without success. This patient had a second child later (not part of the study) and the child also had a long umbilical cord. Although details about this delivery were not made available, they were able to save the baby.

Please call me at 781 – 681 – 2267 if there are any further questions.

Sincerely,
debbie

FAX

ORIGINAL

CONFIDENTIAL

Serono

PART OF THE ARES SERONO GROUP

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

Date: 16 August 2000

1

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149
Phone: (301) 827-4260
Fax phone: (301) 827-4267
RE: Ovidrel Clinical SAE Request

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267
Fax phone: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

As discussed this morning, the following is a follow-up to the response faxed to you for the Medical Reviewer on August 14th regarding the 2 patients enrolled in study 7648 with babies with congenital anomalies. Both investigators have been contacted for further information.

Patient 4-03:.

1. **Was the study patient in labor ?** YES, according to the information on the DER.
2. **Was the baby autopsied ?** According to the investigator, no autopsy was performed.

Patient 6-40:

1. **Was a chromosomal analysis performed on the fetus or the parents ?** The investigator confirmed that no chromosomal analysis was performed, either on the fetus or on the parents.

Please call me at 781 – 681 – 2267 if there are any further questions.

Sincerely, debbie

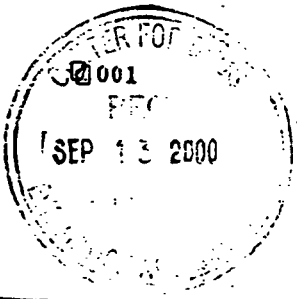
REVIEWS COMPLETED

DSD NOTIFIED

DATE

/18/2000 15:16 FAX

ORIGINAL



FAX

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ORIG AMENDMENT

13M

Serono

PART OF THE ARES SERONO GROUP

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

REVIEW COMPLETED

Date: 14 August 2000

13

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149

Phone: (301) 827-4260

Fax phone: (301) 827-4267

RE: Ovidrel Clinical SAE Request

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267

Fax phone: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie, The following is a response to the Medical Reviewer's request for information on the following patients enrolled in Study 7648:

Patient 4-03 (see DER 34005S96DEU, attached): This 34 year old female patient achieved pregnancy following a cryo-cycle. Based on the information received by DER, the pregnancy continued unremarkably until delivery. During delivery, fetal distress was observed (bradycardia) and an emergency C-section was carried out. Despite the procedure, the child suffered from severe asphyxia (Apgar score not available). The child was transferred to an intensive care unit but died 6 days post-delivery as a result of the perinatal asphyxia. The investigator qualified the event as unrelated to the study drug.

1. **Was the study patient in labor ?** YES, according to the information on the DER.

2. **Was the baby autopsied ?** Based on the information reported by the investigator on the DER, it is not possible to answer this question. The investigator will be contacted and FDA will be notified if there is further information.

Patient 6-40 (see DER 34001S97SWE, attached): This 34 year old female patient achieved pregnancy following ART (ICSI). A severe malformation (acrania) was noted on ultrasound at 16 weeks gestation. An elective termination was decided and performed at 18 weeks gestation. An autopsy of the fetus was carried out and the final diagnosis was Anencephali with hypoplastic adrenals. There are no additional results available. The investigator qualified the event as unrelated to the study drug.

Was a chromosomal analysis performed on the fetus or the parents ? Based on the information provided on the DER, there is no mention of a karyotype exam. A post-mortem study was performed but only a final diagnosis was reported to Serono. The Investigator will be contacted and FDA will be notified if there is further information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT: Serono Laboratories, Inc.	DATE OF SUBMISSION: August 14, 2000
TELEPHONE NO. *(Include Area Code)*: (781) 982-9000	FACSIMILE (FAX) Number *(Include Area Code)*: (781) 878-5001
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 100 Longwater Circle, Norwell, MA 02061	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): NDA 21-149

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: choriogonadotropin alfa for injection	PROPRIETARY NAME *(trade name)* IF ANY: Ovidrel(R)
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*: recombinant human chorionic gonadotropin	CODE NAME *(if any)*

DOSAGE FORM: lyophilized powder for injection	STRENGTHS: 250 mcg	ROUTE OF ADMINISTRATION: subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
Induction of maturation and early luteinization in infertile women pretreated with FSH as part of an ART program (such as IVF) and embryo transfer.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☑ OTHER

REASON FOR SUBMISSION: Response to Request for Information: Updated Package Insert

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1 — THIS APPLICATION IS ☐ PAPER ☑ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 48,934

This application contains the following items: *(Check all that apply)*	
	1. Index
✔	2. Labeling (check one) ☑ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4)) Not Applicable
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
✔	19. OTHER (Specify) Response to Request for Information: Updated Package Insert

CERTIFICATION

agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Pamela Williamson Joyce Vice President, Regulatory Affairs	August 14, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
100 Longwater Circle, Norwell, MA 02061	(781) 982-9000

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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Please DO NOT RETURN this form to this address.

FORM FDA 356h (7/97)

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SERONO LABORATORIES, INC.
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

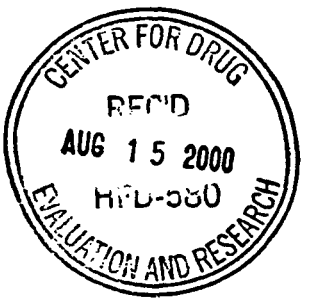
August 14, 2000

ORIG AMENDMENT

DUPLICATE

B2

Susan Allen, M.D., Acting Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 21-149
Ovidrel® (choriogonadotropin alfa for injection)
Request for Information: Updated Package Insert

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a fax from Ms. E. DeGuia to Serono on August 1, 2000 whereby edits and comments to the draft package insert were made.

Herewith, please find the revised draft annotated package insert, as requested. For clarity, the version with edits and comments sent by the Division is provided in Attachment 1. Additionally, for the convenience of the reviewers, the label is provided in both paper and electronic formats.

Please note that the following sections have been updated, as noted by highlighted gray text throughout the document:

Clinical Section:

1. [redacted] has been removed from the "How Supplied" section of the label. The [redacted] has been removed as well.

2. Reference to [redacted] mcg has been deleted from the efficacy tables and text, as requested. Efficacy and Safety information on Ovidrel® 250 mcg is provided in the tables. Where relevant, we have included statements in the text regarding serious adverse events experienced with the 500 mcg dosage; namely OHSS and congenital anomalies.

3. Reference to u-hCG [redacted] has been retained in the efficacy and adverse event tables, as in the PK table. Urinary-derived hCG is a product prescribed in units for over 30 years. Serono feels strongly that some comparative information to u-hCG must be provided to physicians in order that they make informed decisions about the use of this product, which is labeled in mass (mcg). We respectfully request your agreement to leave the u-hCG data obtained by clinical trials in the tables. However, all reference to [redacted] (e.g, statements of Ovidrel® efficacy when compared to [redacted] has been removed from the text.

4. Patient numbers (and percentages) have been added to the tables, as requested.

5. Table 7 has been updated with the delivery information from the remaining 5 patients in Study 8209, as in Appendix 16.1.9 of Section 11.4.1.9 of the Study 8209 Final Report submitted on April 7, 2000. The line, [redacted] has thus been removed.

Chemistry:

6. The term, "choriogonadotropin alfa" has been replaced by "choriogonadotropin alfa for injection" throughout the label, as requested..

7. A statement regarding the similarity between human and recombinant hCG has been added beginning on line 11.

8. A statement regarding how the biological activity was determined, including reference standard for calibration is included beginning on line 23.

9. The pH of the product has been added on line 32.

10. "Mix gently. Do no Shake" in bolded text has been added to the "Administration" section of the label beginning on line 352.

11. Storage conditions have been updated beginning on line 362.

Biopharm:

12. The PK section has been modified according to suggestions beginning on line 47. Table 1 now refers to PK parameters obtained from healthy female volunteers.

13. [redacted] has been added, as requested beginning on line 64.

14. Suggested modifications to the wording in the Metabolism and Pharmacodynamics sections have been added on lines 71 and 77, respectively.

Pharm/Tox:

15. The statement regarding [redacted] death and impaired parturition in rats has been added, as suggested to the "Pregnancy" section beginning on line 274.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267, or the undersigned at 781-681-2298.

Yours sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

Enclosure: diskette
cc: Eufrecina DeGuia (Desk Copy)

FAX

ORIGINAL

serono

CONFIDENTIAL

Date: 09 August 2000

1

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

ORIG AMENDMENT

DM

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149

Phone: (301) 827-4260

Fax phone: (301) 827-4267

CC:

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2267

Fax phone: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

This fax serves as written confirmation for the Medical Reviewer of an error noted in the Ovidrel NDA file 21-149 (ISE, volume 38, page 299) where a statement was made that in Study 7648 there were 7 cases of OHSS with r-hCG and 6 cases with u-hCG.

Please accept that the sentence should have read that the above-mentioned patients had any individual symptom of OHSS, as described in the 7648 Study Report, Appendix 16.4.35.

For clarity, only 2 patients (1 r-hCG: patient 7-17 and 1 u-hCG: patient 3-31) had OHSS, as described in the 7648 Study Report Appendix 16.4.36.

My sincere apologies for the confusion that this error has caused.

Please call if you have questions: 781-681-2267

debbie

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FAX (781) 871-6754

August 7, 2000

ORIGINAL

Susan Allen, M.D., Acting Director,
Division of Reproductive and Urologic
Drug Products, HFD 580 (Room 17B45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

NDA 21-149
Ovidrel® (choriogonadotropin alfa)
Response to Request for Information: CMC

1SC

Dear Dr. Allen,

Reference is made to Ovidrel® NDA 21-149 submitted on November 23, 1999. Further reference is made to a CMC Information Request Letter from the Agency dated July 31, 2000. Accordingly, please find herewith the information as requested by the Chemistry Reviewer in the above-mentioned letter. For reference, the July 31, 2000 letter from the Agency can be found in Appendix 1.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate, at (781) 681 2267 or the undersigned at (781) 681 2298.

Yours Sincerely,

Pamela Williamson Joyce
Vice President,
Regulatory Affairs

enclosure
cc: Ms. E. DeGuia (Desk Copies)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

serono

FAX

ORIGINAL

CONFIDENTIAL

Date: 04 August 2000

14

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

ORIG AMENDMENT
BM

To: Ms. Freshnie DeGuia
(HFD-580)

re: Ovidrel NDA 21-149
Phone: (301) 827-4260
Fax phone: (301) 827-4267
CC:

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs
Phone: (781) 681 - 2267
Fax phone: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

This fax serves as clarification of the Medical Reviewer's questions regarding the Ovidrel OI Study Report (8209). A copying error occurred in that an "Errata List 2" for Study report 8209 was issued which was inadvertently omitted in the copy provided to FDA. Please see Errata List 2 for the 8209 study report (attached). The denominator in the AE tables (Table 33) was corrected and the figures in the tables now match those provided in the Ovidrel label.

1. **Table 33 of the 8209 Study Report lists AE's occurring after hCG. What do the percentages in the table represent?**

   In each cell of the table, there are the number of AE's reported, the number of patients who had those AE's, and the % of patients exposed who had the AE's. For example, in the first line (injection site bruising), there were 11 AE's occurring in 10 patients and 10 patients/198 treated is 5.1%.

2. **Table 23 of the 8209 Study Report states that 2 of 14 deliveries were multiple births. However, our package insert states that 2 of 15 deliveries were multiple births.**

   This table was produced before the results of the final 5 pregnancies were known. In the report, it was noted that the outcomes of 5 ongoing pregnancies were not known at the time of writing. All patients who had such pregnancies were included in the analyses as far as possible and are highlighted in the "Ongoing Pregnancies" row of Table 23. Please refer to Appendix 16.1.9. "Documentation of statistical methods: Pregnancies: How the 5 ongoing pregnancies progressed" (§11.4.1.9.). (attached). One of the last 5 deliveries was an Ovidrel patient who delivered twins. **Therefore 2 of 15 is correct.**

My apologies for any confusion. Please call if you have questions: 781-681-2267 debbie