

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-322**

**Chemistry Review(s)**

**NDA 21-322**

**LUVERIS™, Vial  
(Lutropin alfa for Injection)**

**SERONO, INC.**

**SWAPAN K. DE**

**DIVISION OF REPRODUCTIVE & UROLOGIC DRUG  
PRODUCTS (HFD-580)**

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# Chemistry Review Data Sheet

1. NDA 21-322
2. REVIEW # 2
3. REVIEW DATE: 20-SEP-2004 (revised)
4. REVIEWER: Swapan K. De
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Resubmission

Amendment (carton and container labels)

Amendment (Response to the recommended change in carton and container labels)

Document Date

25-MAY-2004

11-JUNE-2004

29-SEPT-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Serono, Inc.

Address: 100 Longwater Circle  
Norwell, MA 02061

Representative: N/A

Telephone: (781) 681-2273

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUVERIS™ Vial

b) Non-Proprietary Name (USAN): Lutropin alfa for injection

c) Code Name/# (ONDC only): N/A

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Hormone, stimulating multiple ovarian follicular growth for the development of multiple follicles in ovulatory patients participating in a Assisted Reproductive Technology program and induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and is not due to a primary ovarian failure.

11. DOSAGE FORM: Lyophilized powder for injection

13. ROUTE OF ADMINISTRATION: Subcutaneous (SC) injection

12. STRENGTH/POTENCY: 75 IU per vial

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

- SPOTS product – Form Completed  
 Not a SPOTS product  
 Not a SPOTS product

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

See chemistry review #1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: All DMFs related to this application are reviewed and adequate to support this NDA (see chemistry review #1)

B. Other Documents: See chemistry review #1

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	07-July-2007	Office of Compliance
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Will be initiated		Swapan K. De
OPDRA	Acceptable	17-Dec-2001	Alina R. Mahmud, RPh.

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

EA	Categorical exclusion granted	01-May-2001	David T. Lin, Ph.D.
Microbiology	Adequate	11-Feb-2002	Bryan Riley, Ph.D.

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  
 No If no, explain reason(s) below:

Appears This Way  
On Original

# The Chemistry Review for NDA 21-322

## The Executive Summary

### I. Recommendations

- A. From chemistry, manufacturing, and controls point of view, this NDA may be approved. The pending labeling and establishment evaluation report issues are resolved and adequate to support this NDA.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product and Drug Substance(s):

**Dosage form:** Lyophilized powder for injection  
**Strength:** Luveris™ 75 IU  
**Route of Administration:** Subcutaneous Injection

**Description:**

Luveris™ is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP. Each vial contains 82.5 IU lutropin alfa [recombinant human luteinizing hormone (rhLH)], equivalent to 3.7 µg r-hLH, and when reconstituted will deliver 75 IU (3.4 µg) of rhLH. The formulation contains 0.1 mg L-methionine, 47.75 mg sucrose, 0.05 mg polysorbate 20, 0.825 mg disodium phosphate dihydrate, 0.052 mg sodium dihydrogen phosphate monohydrate, and phosphoric acid and/or sodium hydroxide to adjust the pH. The L-methionine

is contained in a 10 mL glass vial, and lyophilized to yield the final product as a white pellet. The vials are sealed with a rubber stopper and capped by an aluminum seal ring and flip-off cap. All manufacturing operations and release testing, except for the bioassay test, are conducted at Laboratoires Serono S.A. (LSA) in Aubonne, Switzerland. The bioassay test is performed at

Product quality from Microbiology point of view is acceptable.

The proposed specifications are acceptable. The relevant DMFs have been reviewed and are adequate for this drug product. Based on the stability data provided, an 18-month expiry date is granted, when stored at 25°C or at refrigerated conditions. OPDRA has determined that the tradename, Luveris™, is acceptable. In addition, adequate chemistry information is presented in the labeling and labels of primary, secondary as well as carton packaging.

Executive Summary Section

Drug Substance:

Luteinizing hormone is a protein hormone whose pharmacodynamic action is mediated through its binding to its surface-bound receptor on target cells leading to increased adenylate cyclase activity. Recombinant human luteinizing hormone is a heterodimer glycoprotein, composed of two noncovalently linked identical subunits, designated as  $\alpha$  and  $\beta$ . The  $\alpha$ -subunit, which is common to all the gonadotropin hormones, is 92 amino acids in length and possesses two sites of N-linked glycosylation (Asn 52 and Asn 78). The  $\beta$ -subunit, which is hormone specific, is 121 amino acids in length and possesses a single site of N-linked glycosylation (Asn 30). No O-glycosylation sites have been detected. [

] Standard recombinant DNA techniques were used to isolate and clone the  $\alpha$  and  $\beta$ -subunit genes into expression vectors and transfect into a standard CHO host cell line.

After transfection of both the  $\alpha$ -subunit and  $\beta$ -subunit expression vectors into a CHO cell line, a final clone, [ ] was isolated [

] This clone was used to establish the Master Cell Bank (MCB). This production cell line was extensively characterized genotypically and phenotypically. [

] proposed specifications are acceptable. The proposed re-test period of [ ] when stored at  $-20 \pm 5^\circ\text{C}$  is acceptable.

**B. Description of How the Drug Product is Intended to be Used**

Luveris is a sterile, lyophilized powder intended as a subcutaneous injection after reconstitution in Sterile Water for Injection, USP. Each vial of drug product contains 82.5 IU lutropin alfa (r-hLH), which after reconstitution with diluent, will deliver 75 IU of r-hLH. The drug product has an expiration date of 18 months and can be stored under refrigerated ( $2^\circ\text{C}$ ) or room temperature ( $25^\circ\text{C}$ ) conditions.

# CHEMISTRY REVIEW

## Executive Summary Section

### C. Basis for Approvability or Not-Approval Recommendation

There are no pending approvability regarding chemistry, manufacturing, and controls issues. Therefore, this NDA is may be approved.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

HFD-580/S. K. De, Ph.D.  
HFD-580/M.J. Rhee, Ph.D.  
HFD-580/A Reddy

### C. CC Block

HFD-580/Division File/NDA 21-488  
HFD-580/S. K. De, Ph.D.  
HFD-580/M.J. Rhee, Ph.D.  
HFD-580/ A. Reddy

1   Page(s) Withheld



       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**NDA:** 21-322  
**Drug:** Luveris® (lutropin alfa for injection)  
**Sponsor:** Serono, Inc.

**Microbiology Efficacy review**

This new drug application did not require a microbiology efficacy review.

*Appears This Way  
On Original*

# CHEMISTRY REVIEW

## Executive Summary Section

### Establishment Evaluation Report:

An EER was resubmitted for this application on 15-June-2004 and the Office of Compliance issued an overall Acceptable recommendation on 07-July-2004 (see below).

14-SEP-2004

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Page 1 of 3

Application:	NDA 21322/000	Action Goal:	
Stamp:	01-MAY-2001	District Goal:	27-SEP-2004
Regulatory Due:	26-NOV-2004	Brand Name:	LUVERIS (LUTROPIN ALPHA)
Applicant:	SERONO INC 1 TECHNOLOGY PL ROCKLAND, MA 02370	Estab. Name:	INJ 75IU
Priority:	3S	Generic Name:	LUTROPIN ALFA
Org Code:	580	Dosage Form:	(FOR INJECTION)
		Strength:	75 IU

Application Comment: THIS DRUG PRODUCT CONTAINS AS THE API A PROTEIN PRODUCED THROUGH RECOMBINANT DNA TECHNOLOGY. [NOTE: I AM STILL TRYING TO FIND OUT WHO PERFORMS RELEASE AND STABILITY TESTING FOR THE DRUG PRODUCT] (on 20-JUN-2001 by D. LIN (HFD-830) 301-827-2003)

FDA Contacts: A. REDDY (HFD-580) 301-827-7514 , Project Manager  
S. DE , Review Chemist  
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 07-JUL-2004 by J. D AMBROGIO (HFD-322) 301-827-9049  
ACCEPTABLE on 14-FEB-2002 by GARCIA M

Establishment: CFN [ ] FEI [ ]  
J

DMF No: AADA:  
Responsibilities: [ ]  
Profile: SVT OAI Status: NONE

Estab. Comment: [ ] J

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-JUN-2001				LINDAV
SUBMITTED TO DO	21-JUN-2001	10D			FERGUSONS
DO RECOMMENDATION	23-JUL-2001			ACCEPTABLE BASED ON FILE REVIEW	CEVERLY

THE MOST RECENT INSPECTION OF THE FIRM (2/2001) WAS ACCEPTABLE FOR ALL PROFILE CLASSES.  
— KNOWS OF NO REASON WHY THE APPLICATION SHOULD NOT BE APPROVED

CARYN EVERLY  
PRE-APPROVAL MANAGER  
OC RECOMMENDATION 23-JUL-2001 ACCEPTABLE DAMBROGIOJ  
DISTRICT RECOMMENDATION  
SUBMITTED TO OC 15-JUN-2004 DES  
SUBMITTED TO DO 15-JUN-2004 10D DAMBROGIOJ  
DO RECOMMENDATION 06-JUL-2004 ACCEPTABLE CEVERLY

# CHEMISTRY REVIEW

## Executive Summary Section

14-SEP-2004

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

Page 2 of 3

RECOMMENDS APPROVAL OF THIS APPLICATION BASED ON THE FIRM'S ACCEPTABLE PROFILE STATUS. KNOWS OF NO REASON WHY THIS APPLICATION SHOULD NOT BE APPROVED.

CARYN MCNAB, PAI MANAGER  
OC RECOMMENDATION

07-JUL-2004

ACCEPTABLE  
DAMBROGIOJ  
DISTRICT RECOMMENDATION

Establishment: CPN 9692032 FEI 3002807447  
LABORATORIOS SERONO SA  
AUBONNE, , SZ

DMF No: AADA:  
Responsibilities: DRUG SUBSTANCE MANUFACTURER  
DRUG SUBSTANCE RELEASE TESTER  
FINISHED DOSAGE MANUFACTURER

Profile: CBI OAI Status: NONE

Estab. Comment: API MANUFACTURER. (on 07-JUN-2001 by D. LIN (HPD-830) 301-827-2003)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-JUN-2001				LINDAV
OC RECOMMENDATION	25-JUN-2001			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	15-JUN-2004				DES
SUBMITTED TO DO	15-JUN-2004	GMP			ADAMSS
DO RECOMMENDATION	24-JUN-2004			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	24-JUN-2004			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Profile: SVS OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURING SITE. SITE OF RELEASE TESTING. ALSO SITE OF STABILITY TESTING. PERFORMS ALL RELEASE AND STABILITY TESTS EXCEPT FOR THE BIOASSAY. (on 29-JUN-2001 by D. LIN (HPD-830) 301-827-2003)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-JUN-2001				LINDAV
SUBMITTED TO DO	25-JUN-2001	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	25-JUN-2001	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	07-NOV-2001		26-NOV-2001		TRIVERA
INSPECTION PERFORMED	26-NOV-2001		26-NOV-2001		GARCIA M
DO RECOMMENDATION	25-JAN-2002			ACCEPTABLE	GARCIA M



-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

Swapn De  
10/7/04 10:02:10 AM  
CHEMIST

Moo-Jhong Rhee  
10/7/04 10:11:07 AM  
CHEMIST  
I concur

**NDA:** 21-322  
**Drug:** Luveris® (lutropin alfa for injection)  
**Sponsor:** Serono, Inc.

**Methods Validation**

The Methods Validation will be requested upon approval.

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On Original

**NDA 21-322**

**Luveris™ (lutropin alfa for injection)**

**Serono, Inc.**

**David T. Lin, Ph.D.  
Division of Reproductive and Urologic Drug Products (HFD-  
580)**

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# Chemistry Review Data Sheet

1. NDA 21-322
2. REVIEW #: 1
3. REVIEW DATE: 29-JAN-2002
4. REVIEWER: David T. Lin, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

none

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original  
Amendment  
Amendment  
Amendment  
Amendment  
Amendment  
Amendment  
Amendment  
Amendment  
Amendment

Document Date

01-MAY-2001  
26-JUN-2001  
17-JUL-2001  
22-OCT-2001  
07-NOV-2001  
20-NOV-2001  
26-NOV-2001  
30-JAN-2002  
11-FEB-2002  
13-FEB-2002

7. NAME & ADDRESS OF APPLICANT:

Name: Serono, Inc.

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

Address: 100 Longwater Circle  
Norwell, MA 02061

Representative: N/A

Telephone: 781-681-2273

#### 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Luveris™ Vial
- b) Non-Proprietary Name (USAN): Lutropin alfa for injection
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 3
  - Submission Priority: S

#### 9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Hormone, stimulating multiple ovarian follicular growth for the development of multiple follicles in ovulatory patients participating in a Assisted Reproductive Technology program and induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and is not due to a primary ovarian failure

11. DOSAGE FORM: Lyophilized powder for injection (in vial)

12. STRENGTH/POTENCY: 75 IU per vial

13. ROUTE OF ADMINISTRATION: Subcutaneous (SC) injection

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

SPOTS product – Form Completed

Not a SPOTS product

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

See page 7

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
1	3			3	Adequate	2/27/01	Reviewed by Dr. C-H Niu
1	3			3	Adequate	3/31/97	Reviewed by Dr. M. Shaikh

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA	NDA 20-378	Serono's approved NDA for Gonal-F® [follitropin alfa (rDNA origin) for injection]; approved 9/29/97
Original NDA	NDA 20-604	Serono's approved NDA for Serostim® [somatropin (rDNA origin) for injection]; approved 8/23/96
Original NDA	NDA 21-149	Serono's approved NDA for Ovidrel (choriogonadotropin alfa for injection); approved 9/20/00
Original NDA	NDA 21-149	The sterile diluent (Water for Injection ,USP in 2 mL vial)

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

		supplied by <input type="checkbox"/> J was reviewed and determined to be acceptable to support the NDA.
--	--	---

## 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	2/14/02	M. Garcia
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Will be initiated	2/8/02	David Lin, Ph.D.
OPDRA	Acceptable	12/6/01	
EA	Categorical exclusion granted	5/1/01	David Lin, Ph.D.
Microbiology	Approval	1/30/02	Bryan Riley, Ph.D.

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**Chemistry Review Data Sheet**

**Structure:**

Recombinant human luteinizing hormone (rhLH) is composed of alpha and beta subunits, which are bound together in a non-covalent association of high affinity without interchain disulfide bonds or covalent bonds. The alpha subunit is common to all four members of a glycoprotein hormone family, including pituitary follicle stimulating hormone (FSH), pituitary thyroid stimulating hormone (TSH) and placental human chorionic gonadotropin (hCG). The amino acid sequences for the beta subunit, which determines the specific biological properties of the heterodimer, are different among the four glycoprotein hormones.

**Alpha Subunit:**

The alpha subunit consists of 92 amino acid residues. Structurally, there are two glycosylation sites (Asn 52 and 78, see underlined and bolded amino acid residues below) and five internally cross-linked disulfide bonds. The molecular weight is estimated to be approximately 23,000 dalton.



**Beta Subunit:**

The beta subunit consists of 121 amino acid residues with one glycosylation site (Asn 30, see underlined and bolded amino acid residue below) and six internally cross-linked disulfide bonds. The molecular weight is estimated to be approximately 18,000 dalton.



# The Chemistry Review for NDA 21-322

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From chemistry, manufacturing, and controls point of view, this NDA is may be **Approved**.

However, there are some minor CMC labeling recommendations that are not approvability issues that need to be addressed by the sponsor.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

**Luveris™** is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP. Each vial contains **82.5 IU lutropin alfa [recombinant human luteinizing hormone (r-hLH)]**, equivalent to 3.7 µg r-hLH, and when reconstituted will deliver 75 IU (3.4 µg) of r-hLH. [

] The formulation contains 0.1 mg L-methionine, 47.75 mg sucrose, 0.05 mg polysorbate 20, 0.825 mg disodium phosphate dihydrate, 0.052 mg sodium dihydrogen phosphate monohydrate, and phosphoric acid and/or sodium hydroxide to adjust the pH. The L-methionine [

] The drug product is manufactured as a sterile solution, filled into [ ] glass vials, and lyophilized to yield the final product as a white pellet. The vials are sealed [

] rubber stopper and capped by an aluminum seal ring and flip-off cap. All manufacturing operations and release testing, except for the bioassay test, are conducted at Laboratoires Serono S.A. (LSA) in Aubonne, Switzerland. The bioassay test is performed at [

] Product quality from Microbiology point of view is acceptable. [

The proposed specifications are acceptable. ]

The relevant DMFs for the glass vial and rubber stopper have been reviewed and determined to be adequate as a container/closure system for this drug product. In addition, the Microbiology Reviewer has determined the integrity of the container/closure system to be acceptable.

**Executive Summary Section**

Based on the stability data provided, an 18-month expiry date is granted, when stored at 25°C. However, storage under refrigerated conditions is also acceptable since the product is contained in a sealed glass vial. OPDRA has determined that the tradename, Luveris™, is acceptable. In addition, adequate chemistry information is presented in the labeling and labels of primary as well as secondary packaging labels.

**Drug Substance:**

Luteinizing hormone is a protein hormone whose pharmacodynamic action is mediated through its binding to its surface-bound receptor on target cells leading to increased adenylate cyclase activity.

Recombinant human luteinizing hormone is a heterodimer glycoprotein, composed of two non-covalently linked identical subunits, designated  $\alpha$  and  $\beta$ . The  $\alpha$ -subunit, which is common to all the gonadotropin hormones, is 92 amino acids in length and possesses two sites of N-linked glycosylation (Asn 52 and Asn 78). The  $\beta$ -subunit, which is hormone specific, is 121 amino acids in length and possesses a single site of N-linked glycosylation (Asn 30). No O-glycosylation sites have been detected.

└

Standard recombinant DNA techniques were used to isolate and clone the  $\alpha$ - and  $\beta$ -subunit genes into expression vectors and transfect into a standard CHO host cell line. ]

transfection of both the  $\alpha$ -subunit and  $\beta$ -subunit expression vectors into a CHO cell line, a final clone, designated [ ] was isolated [ ] This clone was used to establish the Master Cell Bank (MCB). This production cell line was extensively characterized genotypically and phenotypically. ]

The production process [ ] a purification process [ ] Both of these operations are conducted at Laboratoires Serono S.A. in Aubonne, Switzerland. Release testing is also performed at the same site, except for the bioassay test, which is performed at [ ]

Executive Summary Section

11

] The proposed specifications are acceptable.

The proposed re-test period of 12 ] when stored at  $-20 \pm 5^{\circ}\text{C}$  is acceptable.

**B. Description of How the Drug Product is Intended to be Used**

Luveris™ is a sterile, lyophilized powder intended as a subcutaneous injection after reconstitution in Sterile Water for Injection, USP. Each vial of drug product contains 82.5 IU lutropin alfa (r-hLH), which after reconstitution with diluent, will deliver 75 IU of r-hLH. Luveris™ is co-administered with recombinant human follicle-stimulating hormone (r-hFSH) to stimulate development of a competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

The drug product has an expiration date of 18 months and can be stored under refrigerated ( $2^{\circ}\text{C}$ ) or room temperature ( $25^{\circ}\text{C}$ ) conditions.

**C. Basis for Approvability or Not-Approval Recommendation**

There are no pending approvability chemistry, manufacturing, and controls issues. Therefore, this NDA is may be approved.

The only CMC issues that have not been fully resolved are minor revisions to the package insert and the container/carton labels.

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**III. Administrative**

**A. Reviewer's Signature**

**B. Endorsement Block**

ChemistName/Date: DLin/  
ChemistryTeamLeaderName: DWu/  
ProjectManagerName: AReddy

**C. CC Block**

HFD-580/Division File/NDA 21-322  
HFD-580/D.T. Lin, Ph.D.  
HFD-580/A. Reddy, M.P.H.

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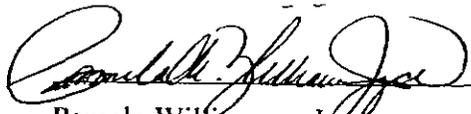
§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

**17. FIELD COPY CERTIFICATION**

The undersigned hereby certifies that the field copy of the Chemistry, Manufacturing, and Controls section of this New Drug Application (NDA) is a true copy of the information contained in the archival and review copies of this NDA.

  
\_\_\_\_\_  
Pamela Williamson Joyce  
Vice President, Regulatory Affairs

10 April 01  
Date

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NDA 21-322

Luveris (lutropin alfa for injection) 75 I.U.

Serono, Inc.

**Statistics review(s) and memoranda regarding dissolution and stability**

The Statistical review is included in reviews #1 and #2 of DMF C

J

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2/6/02

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       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

NDA 21-322  
Luveris (lutropin alfa for injection) 75 I.U.  
Serono, Inc.

**Environmental Assessment**

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b), as amended in the 29-Jul-1997 Federal Register. This was found to be satisfactory (see Chemistry Review # 1 dated February 5, 2002)

*CUA*  
*2/5/02*

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Luveris (lutropin alfa for injection) 75 I.U.  
Serono, Inc.

**Micro (validation of sterilization) Review(s) and Memoranda**

This is not a sterile product. No microbiology review is required.

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Luveris (lutropin alfa for injection) 75 I.U.  
Serono, Inc.

**EES**

There were no manufacturing changes. No EER is required.

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Luveris (lutropin alfa for injection) 75 I.U.

Serono, Inc.

**Methods Validation**

Methods validation pending.

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2/07/02

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NDA 21-322

Luveris (lutropin alfa for injection) 75 I.U.

Serono, Inc.

**Memo from DSI regarding GLP inspection (if any)**

No GLP inspection was needed from DSI for this drug product.

*MR*  
*2/6/02*

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