CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-765

CHEMISTRY REVIEW(S)

NDA 21-765

Tradename
(follitropin alfa for injection)

Serono, Inc.

Yvonne Yang, Ph.D.

Division of Reproductive and Urologic Drug Products
HFD-580

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-765

2. REVIEW #: #1

3. REVIEW DATE: Mar-22-2004

4. REVIEWER: Yvonne Yang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-765	Mar-11-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Serono Inc.
Address:	One Technology Place Rockland MA 02370
Representative:	Pamela Williamson Joyce, RAC
Telephone:	(781) 681-2273 or (781) 681-2298

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename
b) Non-Proprietary Name (USAN): Follitropin 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: Gonadotropins

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 37.5 IU (2.8 µg) per vial
75 IU (5.5 µg)
150 IU (11 µg)

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: ____X____ Rx _____ OTC

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

____X____ SPOTS product – Form Completed

_____ Not a SPOTS product

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

Chemical Name: recombinant human follicle stimulating hormone (r-hFSH)
Follitropin alfa (alpha-subunit): $C_{437}H_{682}N_{122}O_{134}S_{13}$ MW = 10,205.88 Da
Follitropin alfa (beta-subunit): $C_{538}H_{833}N_{145}O_{171}S_{13}$ MW = 12,485.34 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate	Aug-26-2003	Reviewed by Jean Salemme
	III			3	Adequate	Feb-27-2001	Reviewed by Chien-Hua Niu
	III			3	Adequate	Sept-14-2001 Apr-19-2002 (of similar product)	Reviewed by Yvonne Yang

[1] 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")

[2] 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
NDA	20-378, SCF-015	Gonal-f® (follitropin alfa for injection)
NDA	20-378, SE-032	Gonal-f® (follitropin alfa for injection)

18. STATUS:

ONDC:

CONSULTS / CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	N/A (see pp. 11-13 of this review)		Yvonne Yang
Microbiology	Recommend Approval on the basis of product quality microbiology	Dec-06-2001	Bryan S. Riley
EA	Categorical exclusion granted		Yvonne Yang
Methods Validation	To be validated by FDA laboratories		Yvonne Yang
Pharm/Tox	N/A		
Biopharm	N/A		
Biometrics	N/A		
ODS/DMETS	Pending Tradename review		

19. ORDER OF REVIEW N/A

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-765

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-765 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls.

Note: NDA 21-765 Tradename (follitropin alfa for injection) was created as a result of the finding that the new formulation submitted in supplement SCF-015 to NDA 20-378 was not bioequivalent to the approved products in that NDA. A clinical study was subsequently performed for the new formulation; therefore, a new NDA is required.

For chemistry, manufacturing and controls information, refer to NDA 20-378 for the parts that have not been changed, and to supplement SCF-015 for changes regarding the filled-by-mass manufacturing process, the container/closure system, and the diluent (Water for Injection, USP; in pre-filled syringes).

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:

Tradename (follitropin alfa for injection) is a new formulation for the currently approved Gonal-f® (NDA 20-378). Tradename is supplied in the form of sterile, lyophilized powder for injection in single-dose vials filled with 41 IU (3 µg), 82 IU (6 µg), or 165 IU (12 µg) to deliver 37.5 IU (2.8 µg), 75 IU (5.5 µg), or 150 IU (11 µg) of follitropin alfa, respectively. Each vial of Tradename also contains 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, and 0.05 mg polysorbate 20. O-phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment. Tradename is manufactured using the fill-by-mass process.

The formulation for Tradename (follitropin alfa for injection) differs from that for Gonal-f® (follitropin alfa for injection) in the addition of two inactive ingredients: methionine and polysorbate 20. The amount of the oxidized α-subunits in Tradename, in the new formulation containing methionine and polysorbate 20, appears to increase minimally after long-term storage. Available stability data for Tradename support an expiry of 24 months when stored at 25±2 °C.

Tradename single-dose vials are available in six different configuration of packages containing one or ten vials of follitropin alfa for injection (37.5 IU, 75 IU, or 150 IU), one or ten pre-filled syringes containing the diluent (Sterile Water for Injection, USP), one 18-gauge reconstitution needle, and one 27-gauge administration needle (see configuration shown in table below).

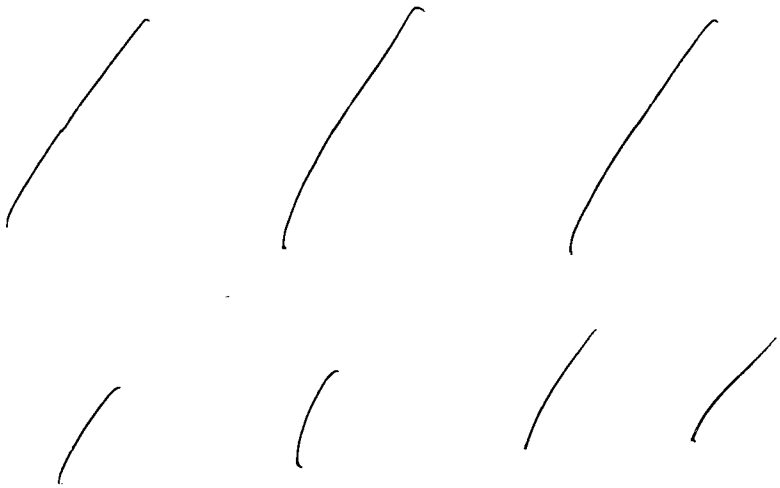
Packaging	Vial (Follitropin alfa)	Pre-Filled Syringe (Diluent)	Reconstitution Needle (18 gauge)	Administration Needle (27 gauge)
NDC 44087-9025-1	1 x 37.5 IU	1	1	1
NDC 44087-9025-6	10 x 37.5 IU	10	1	1
NDC 44087-9005-1	1 x 75 IU	1	1	1
NDC 44087-9005-6	10 x 75 IU	10	1	1
NDC 44087-9010-1	1 x 150 IU	1	1	1
NDC 44087-9010-6	10 x 150 IU	10	1	1

Drug Substance:

The drug substance follitropin alfa (recombinant human follicle stimulating hormone, r-hFSH) is a glycoprotein produced in genetically engineered Chinese Hamster Ovary (CHO) cells in which the genes encoding for the alpha- and beta-subunits of r-hFSH were introduced through recombinant DNA technology.

purified by conventional chromatography.

Follitropin alfa is composed of two polypeptide subunits (α- and β-) bound together non-covalently. The α-subunit is common to all four members of a glycoprotein hormone family, including pituitary luteinizing hormone (LH), pituitary thyroid stimulating hormone (TSH), and placental human chorionic gonadotropin (hCG). The amino acid sequences for β-subunit, which determines the specific biological properties of the heterodimer, are different among the 4 glycoprotein hormones. The α-subunit consists of 92 amino acids. The β-subunit consists of 111 amino acids, (see CMC review #1 for NDA 20-378 for the primary amino acid sequences for the α- and β-subunits).



The biological activity of follitropin alfa is measured using the European Pharmacopoeia rat ovarian weight gain assay in female Sprague-Dawley rats (Steelman and Poley method, 1953). The *in vivo* biological activity of follitropin alfa has been calibrated against the 1st International Standard for Recombinant Human Follicle Stimulating Hormone established in 1995 by the Expert Committee on Biological Standards of the World Health Organization. The specific activity of follitropin alfa, expressed in IU/mg of protein, is obtained by calculating the ratio between the *in vivo* biological activity (in IU) and the protein content (in mg) as measured by the Lowry method.

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

Tradename is supplied in single-dose vials containing lyophilized powder of follitropin alfa, and the diluent (Sterile Water for Injection, USP) in a pre-filled syringe. Tradename vials containing lyophilized follitropin alfa may be stored refrigerated or at room temperature (2-25 °C/36-77 °F), and protect from light.

Tradename single-dose vials are filled with 41 IU (3 µg), 82 IU (6 µg), or 165 IU (12 µg) to deliver 37.5 IU (2.8 µg), 75 IU (5.5 µg), or 150 IU (11 µg) of follitropin alfa, respectively. The dose to be administered and the dosing schedule should be determined by the physician. The patient should read the Patient Instructions for Use included in the Tradename package before using the product. Tradename should be reconstituted with the diluent immediately before use. If more than one vial of the Tradename is needed for reconstitution, the concentration of the final reconstituted material should not exceed 225 IU/0.5 ml. Tradename is intended to be administered subcutaneously immediately after reconstitution. Any unused reconstituted material should be discarded according to the physician's instructions.

Tradename is indicated for the induction of ovulation and pregnancy in the oligoanovulatory infertile female patients in whom the cause of infertility is functional and not due to primary ovarian failure, and for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology program.

In a letter dated Jan-21-2004, the applicant states that upon approval of this application, NDA 21-765, Tradename will be provided for single-doses of follitropin alfa for injection (37.5 IU, 75 IU, and 150 IU) with the new lyophilized formulation containing ← methionine and polysorbate 20,

However, upon approval of SCS-016, NDA 20-378, Multi-Doses of follitropin alfa for injection (450 IU, and 1050 IU) will be provided in the old formulation.

The characteristics of Tradename (NDA 21-765) and Gonal-f® (NDA 20-378) are summarized in the following table for comparison.

	NDA 21-765	NDA 20-378
Tradename	Tradename (to be submitted)	Gonal-f®
Established Name	Follitropin alfa for injection	Follitropin alfa for injection
Formulation	New Formulation: Follitropin alfa 2.8, 5.5, or 11 µg Sucrose 30 mg $Na_2HPO_4.2H_2O$ 1.11 mg $NaH_2PO_4.H_2O$ 0.45 mg Methionine 0.1 mg Polysorbate 20 0.05 mg o-phosphoric acid qs Sodium hydroxide qs	Currently Approved: Follitropin alfa Sucrose 30 mg $Na_2HPO_4.2H_2O$ 1.11 mg $NaH_2PO_4.H_2O$ 0.45 mg o-phosphoric acid qs Sodium hydroxide qs
Dosage Form	Lyophilized powder for injection	Lyophilized powder for injection
Manufacturing Process	Fill-by-mass (µg)	Fill-by-activity (IU)
Dose Strength	**Single Doses** 37.5 IU (2.8 µg) 75 IU (5.5 µg) 150 IU (11 µg)	**Multi-Doses**:
Diluent	Sterile Water for Injection, USP	Bacteriostatic Water for Injection (0.9% benzyle alcohol), USP
Indications	Two indications only (for female only)	Three indications (for both female and male)

Special Note:

The final labeling and the labels for the container/closure system for NDA 21-765, with the appropriate tradename, need to be re-submitted for review by the Agency.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-765 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls:

- The fill-by-mass manufacturing process does not compromise the quality of the product.
- The quality of the product in the new formulation is considered better than the currently approved formulation with respect to stability.
- Regulatory specifications for Tradename remain unchanged and satisfactory. The new formulation does not compromise the sterility of the product.
- Available real time stability data for Tradename support an expiry of 24 months at 25±2 °C.
- The new container/closure system is comparable to that of the currently approved product.
- EES: See p. 12 of this review

III. Administrative

A. Reviewer's Signature in DFS

B. Endorsement Block in DFS

C. CC Block in DFS

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

/s/

Yvonne Yang
3/25/04 11:52:44 AM
CHEMIST

Moo-Jhong Rhee
3/25/04 01:04:51 PM
CHEMIST
I concur