CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-765

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-765
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	5/27/04
DRUG NAME:	follitropin alpha for injection (r-hFSHα)
INDICATION:	1) induction of ovulation and pregnancy in the oligoanovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure 2) development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program
SPONSOR:	Serono Inc.
DOCUMENTS REVIEWED:	EDR
REVIEW DIVISION:	Division of Reproductive and Urologic Drug Products (HFD-580)
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Daniel Shames, M.D.
PROJECT MANAGER:	Reddy

Date of review submission to Division File System (DFS): March 19, 2004

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: From a Pharmacology/Toxicology viewpoint, NDA 21-765 is recommended for Approval.

B. Recommendation for nonclinical studies: none

C. Recommendations on labeling: Labeling for Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy and Nursing Mothers will be similar to the label for GONAL-f®.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: New excipients, methinine and polysorbate 20, have been used previously in approved drug products and are deemed safe at the concentrations found in this new formulation.

A. Pharmacologic activity: recombinant human follicle stimulating hormone, r-hFSH

B. Nonclinical safety issues relevant to clinical use: none

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 210765
Review number: 1
Sequence number/date/type of submission: N000 dated May 27, 2003
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Serono, Inc.
One Technology Place
Rockland, MA 02370
(781) 681-2273
Manufacturer for drug substance: ?

Reviewer name: Lynnda Reid, Ph.D.
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: March 19, 2004

Drug:

Trade name: ?
Generic name: follitropin alpha for injection; follicle stimulating hormone
Code name: r-hFSHα
Structure: r-hFSH is a human glycoprotein hormone consisting of two non-covalently linked non-identical protein components designated as α and β. The alpha subunit consists of 92 amino acids . The beta subunit consists of 111 amino acids . R-hFSH is derived from a Chinese Hamster Ovary cell line which has been transfected with human genes that encode for the α and β subunits of FSH.

Relevant INDs/NDAs/DMFs: NDA 20-378 (SERONO)

Drug class: gonadotropin

Indication(s):
1) induction of ovulation and pregnancy in the oligoanovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure
2) development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program

Clinical formulation: Lyophilized r-hFSHα powder for injection is supplied in single-dose vials filled with 41 IU (3 µg), 82 IU (6µg) or 165 IU (12 µg) to deliver 37.5 IU (2.8 µg), 75 IU (5.5 µg) or 150 IU (11 µg) of FSHα, respectively. Each vial 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. Contents will be dissolved in Sterile Water for Injection immediately prior to use.

Route of administration: subcutaneous injection

Proposed use:
1) Infertile patients with oligo-anovulation: The recommended initial dose of the first cycle is 75 IU/day. Incremental adjustment in dose of up to 375 IU may be considered after 14 days. Further dose increases of the same magnitude could be made, if necessary, every seven days up to a maximum recommended dose of 300 IU/day. Treatment duration should not exceed 35 days unless an E2 rise indicates imminent follicular development.
2) Assisted Reproductive Technologies: Therapy should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU/day until sufficient follicular development is attained.

Drug History: Follitropin alpha for injection was originally approved under NDA 20-378 (GONAL-f®) for injection of follicular development and ovulation in women with oligo-anovulatory infertility and multiple follicular development in women undergoing assisted reproductive technology (ART) procedures, e.g., in vitro fertilization (IVF)/embryo transfer (IVET). It was subsequently given an orphan drug designation for male hypogonadal hypogonadism (HH).

This NDA constitutes a new formulation for follitropin alpha for injection. In bioequivalency studies, it was found not to be bioequivalent to GONAL-f®, necessatating the submission of a new NDA. It also differs from the original GONAL-f® formulation in the addition of two inactive ingredients: methinine ( ) and polysorbate 20 ( ). Both inactive ingredients have a prior history of use in drug products and are deemed safe.

Safety and efficacy of the new formulation were assessed in clinical studies performed with the new formulation.

Studies reviewed within this submission: None.

Studies not reviewed within this submission: All nonclinical studies are cross-referenced to NDA 20-378.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: From a Pharmacology/Toxicology perspective, we recommend approval.

Unresolved toxicology issues (if any): None

Recommendations: None

Suggested labeling: Labeling for Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy and Nursing Mothers will be similar to the label for GONAL-f®.

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

/s/

Lynnda Reid
3/25/04 09:26:52 AM
PHARMACOLOGIST