CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-684

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-684
Review number: 1
Sequence number/date/type of submission: 000/7-28-2003/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Serono Inc. Rockland, MA
Manufacturer for drug substance:

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: 9-2-03

Drug:

Trade name: Gonal-f Pen

Generic name (list alphabetically): Recombinant Follicular Stimulating Hormone (Follitropin alfa for injection)

Code name: r-hFSH

Chemical name:

CAS registry number:

Mole file number:

Molecular formula/molecular weight:

Structure: The primary structure of follitropin alfa is identical to human follicle stimulating hormone (FSH), a naturally occurring human protein that is derived from the urine of pregnant women.

Relevant INDs/NDAs/DMFs: INDs 38,712

Drug class: gonadotropin

Indication: Induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure and development of multiple follicles in the ovulatory patient participating in an ART (assisted reproductive technologies) program.

Clinical formulation: Gonal-f Pen (follitropin alfa injection) is supplied as a sterile, ready-to-use liquid formulation in a disposable multidose delivery system that will deliver a minimum of 300 IU (22 ug) in 0.5 ml; 450 IU (33 ug) in 0.75 ml, or 900 IU (66 ug) in 1.5 ml r-hFSH. The minimum dose that can be set is 37.5 IU and the maximum dose that can be set is 450 IU (for 450 IU and 900 IU Gonal-f Pens only). The formulation composition/ml of Liquid r-hFSH multidose along with the already approved r-hFSH multidose (Gonal-F Multidose) is given in table below:

Components	Amount Test article Liquid r-hFSH Multidose	Comparative compound r-hFSH Multidose 1200 IU (Gonal-F Multidose)
r-hFSH	40 ug (600 IU)	600 IU
Sucrose	60.0 mg	—
Methionine	100 ug	/
$Na_2HPO_4\ 2H_2O$	1.1	0.55
$NaH_2PO_4\ H_2O$	0.45 mg	0.225 mg
—	0.1 mg	/
—	m-cresol, 3.0 mg	benzyl alcohol.

Thus the only difference in composition for this product from the already approved r-hFSH multidose 1200 IU (Gonal-F Multidose) under NDA20-378 is that the present formulation under NDA 21-684 contains additional methionine and — and has m-cresol instead of benzyl alcohol.
Since all the 3 different strengths are presented in pre-filled glass cartridges that differ only in the filling volume, the concentration of the both the active ingredient and excipients is same in the 0.5, 0.75 and 1.5 ml presentations.

Route of administration: Subcutaneous

Proposed use: As described under Indication

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: Since the present liquid formulation contains r-hFSH similar to that used in the currently approved lyophilized powder formulation (NDA 20-378), and as the dosage, indication and dosing regimen are identical to that of the currently approved Gonal-f, Pharmacology recommends approval of Liquid formulation of r-hFSH Gonal-f (follitropin injection).

B. Recommendation for Nonclinical Studies: A single nonclinical toxicity study entitled "Local tolerability study in rabbits by subcutaneous route" showed that the introduction of two additional excipients, i.e., methionine and replacement of polysorbate 20 by poloxamer 188 , and the benzyl alcohol replaced by m-cresol did not affect the local tolerance profile of the drug product.

C. Recommendations on Labeling: Labeling is similar to that for the currently approved lyophilized Gonal-f formulation under NDA 20-378. Both formulations have similar indications and dosing regimen.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: A full battery of nonclinical pharmacology, pharmacokinetic, and toxicology studies were submitted and reviewed for lyophilized formulation of recombinant human follicle stimulating hormone (Gonal-F) under sponsor's approved NDA 20-378.

B. Pharmacologic Activity: Reviewed under NDA 20-378 for lyophilized r-hFSH (Gonal-F).

C. Nonclinical Safety Issues Relevant to Clinical Use: none

III. Administrative: Pharmacology recommends approval of NDA 21-684.

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

None submitted. See review of NDA 20-378

II. SAFETY PHARMACOLOGY:

None submitted. See review of NDA 20-378

III. PHARMACOKINETICS/TOXICOKINETICS:

None submitted. See review of NDA 20-378

IV. GENERAL TOXICOLOGY:

Study title: Local tolerability study in rabbits by subcutaneous route

Key study findings: The formulation was well tolerated. There were no local effects induced either clinically or at macroscopic examination of the injection sites.

Study no: IMP 23378
Volume #, and page #: 6 of 9, page 1
Conducting laboratory and location:

Date of study initiation: 1-23-2002
GLP compliance: yes
QA report: yes (*) no ( )
Drug, lot #, radiolabel, and % purity: Batch GGC101
Formulation/vehicle: Liquid r-hFSH Multidose 60 ug with 0.3% m-cresol
Batch GGC101. Ready to use cartridges (60 ug/1.5 ml) solution/placebo had the same content of excipient as the test compound. Comparator compound was Freeze-dried r-hFSH Multidose 1200 IU (Gonal-F Multidose). Batch BD001C. Vehicle for the comparator compound was 0.9% benzyl alcohol water solution. Batch OBEX702. Negative control article was 0.9% NaCl sterile solution.

Methods (unique aspects):
Dosing:
Species/strain: rabbit/NZW
#/sex/group or time point (main study): as shown in table below:

Group (route)	No. of animals	Site	Test substance	Volume (ml/site)	Dose	Macroscopic examination (No of animals) Day 3	Day 15
1 (SC)	6	Right	Liquid r-hFSH Multidose	1	40 ug/site (600 IU/site)	3	3
		Left	Placebo	1			
2 (SC)	6	Right	Freeze dried r-hFSH	1	40 ug/site (600 IU/site)	3	3
		Left	Saline solution (negative control article)	1			

The test article, the comparative compound, the placebo and the negative control article were injected as a single administration by the SC route. Each animal was injected at two different sites of the thorax region that had been shaved free of hair.

Satellite groups used for toxicokinetics or recovery: Three animals in each treatment group were killed 2 days after treatment (day 3 of study) and the remaining 3 animals were killed 14 days after dosing (day 15 of study).
Age: 3-4 months
Weight: 2.98 – 3.38 kg males
Doses in administered units: single dose
Route, form, volume, and infusion rate: as given in table

Observations and times:

Clinical signs: daily
Body weights: -
Food consumption: -
Ophthalmoscopy: -
EKG: -
Hematology: -
Clinical chemistry: -
Urinalysis: -
Gross pathology: gross examination of the injection site
Organs weighed: -
Histopathology: not conducted since there was not macroscopic findings
Toxicokinetics: -
Other: -

Results:

Mortality: none
Clinical signs: none
Body weights:-
Food consumption: -
Ophthalmoscopy: -
Electrocardiography: -
Hematology: -
Clinical chemistry:
Urinalysis: -
Organ weights: -
Gross pathology: No macroscopic changes were observed at the subcutis injection sites examined 2 and 14 days after treatment.
Histopathology: not conducted
Toxicokinetics: -

Summary of individual study findings: No clinically appreciable reactions were induced either by Liquid r-hFSH Multidose or by the comparator compound in the subcutaneous injection sites. No macroscopic changes were reported at the injection sites 2 and 14 days after treatment.

Toxicology conclusions: Liquid r-hFSH Multidose was well tolerated when injected by SC route at dose level of 40 ug in 1 ml/site of injection.

Histopathology Inventory for NDA # 21-684
No histological examination was conducted

Study	IMP23457			
Species	rabbit			
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				

Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

V. GENETIC TOXICOLOGY:

None submitted. See review of NDA 20-378

Labeling recommendations: As stated in labeling for the Gonal-f lyophilized formulation i.e., Gonal-F under NDA 20-378.

VI. CARCINOGENICITY:

Not indicated

Labeling Recommendations: Same as for the Gonal-F lyophilized formulation approved under NDA 20-378.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

None submitted. See review of NDA 20-378.

VIII. SPECIAL TOXICOLOGY STUDIES:

None submited

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: Based on preclinical local toxicity study in rabbits with the proposed formulation i.e., Gonal-f Pen and sponsor's currently approved formulation i.e., Gonal-F and sponsor's reports of clinical use for the proposed indications, Liquid r-hFSH Multidose was well tolerated locally.

General Toxicology Issues: none

Recommendations: Pharmacology recommends approval of NDA 21-684 for Liquid r-hFSH Multidose formulation

Labeling with basis for findings: same as for the currently approved sponsor's NDA 20-378 for lyophilized r-hFSH Multidose formulation.

X. APPENDIX/ATTACHMENTS:

Addendum to review: none

Other relevant materials (Studies not reviewed, appended consults, etc.): none

Any compliance issues: none

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/s/

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