CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-765

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-765** (changed from 20-378 S032)	*Brand Name*	/
OCPB Division (I, II, III)	DPE II (HFD 870)	*Generic Name*	r FSH (fill by mass)
Medical Division	DRUDP (HFD 580)	*Drug Class*	Female Gonadotropins
OCPB Reviewer	Dhruba J. Chatterjee, Ph.D.	*Indication(s)*	Assisted Reproductive Technologies (ART) and Ovulation Induction
OCPB Team Leader	Ameeta Parekh, Ph.D.	*Dosage Form*	Injectable powder
Date of Submission	5/27/2003	*Dosing Regimen*	Once daily (for few days during ART procedure)
Estimated Due Date of OCPB Review	3/01/2004	*Route of Administration*	Subcutaneous injection
PDUFA Due Date	3/26/2004	*Sponsor*	Serono Inc.
Division Due Date	3/15/2004	*Priority Classification*	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				

renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**0**		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		• **No specific CPB information submitted**
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)

Memorandum

This original NDA was initially submitted as NDA 20-378 S032 and contained only clinical efficacy and safety information. Based on the review of all the disciplines, OCPB has recommendations only to change certain portion of the product label. No studies related to OCPB were submitted in this application.

Background: Gonal-F was originally approved for the current indication in females, as well in male as a fill by strength (IU) formulation (referred to as Formulation A hereon). Based on the Agency's recommendation, the sponsor developed a fill-by-mass formulation (Formulation B hereon, the subject of this NDA), a formulation that was found bio-*in*-equivalent to formulation A. Sponsor was recommended to submit clinical evidence of safety and efficacy. In this current NDA, sponsor has submitted evidence of clinical safety and efficacy of Formulation B. However, the following issues should be noted in the context of this submission:

- The submitted clinical information is only for the female indication and hence, sponsor needs a separate label relevant to just this current product (for formulation B)
- There is a need for a new brand name (identifier) to separate this product from the already approved formulation A ("Gonal F"), and the sponsor is currently engaged in doing so
- Sponsor has already submitted and received an action on **NDA 21-684** comparing the bioequivalence of a liquid solution (henceforth, formulation C) that essentially is formulation B along with . —) to formulation B. This NDA received an approvable action and its approval is contingent upon the approval of this current NDA 21-765.

Since no PK information was submitted for formulation B in this NDA, the sponsor has included the PK information in the label obtained with formulation B (test formulation) in the bioequivalence trial conducted under NDA 21-684. Submission of this updated information was acceptable. Office of Clinical Pharmacology and Biopharmaceutics has reviewed this amendment and finds it acceptable.

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

/s/

Dhruba Chatterjee
3/23/04 03:55:06 PM
BIOPHARMACEUTICS
Final labeling should accomodate our final comments on 3/23/04

Final labeling comments accepted - acceptable to OCPB.

Ameeta Parekh
3/25/04 08:17:14 AM
BIOPHARMACEUTICS
concur