

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-149

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

SEP 14 2000

New Drug Application
Office of Clinical Pharmacology and Biopharmaceutics Review

Addendum II - Labeling

NDA:	21-149
Type of Submission:	NDA 1/S
Generic Name:	Recombinant Human Chorionic Gonadotropin r-hCG
Formulation(s);	Injection (Freeze-dried)
Strength(s);	250 µg / 1 ml
Route(s)	Subcutaneous Injection
Brand Name:	Ovidrel®
Sponsor:	Serono Laboratories, Inc. Norwell, MA
Submission Date(s):	Latest Labeling Submission: September 13, 2000 Original NDA Submission: November 23, 1999
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. LABELING COMMENTS

This sponsor's labeling revisions dated September 13, 2000 are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. These revisions incorporate changes previously recommended by OCPB and corrects some grammatical errors. OCPB recommends that NDA 21-129 be approved.

II. SIGNATURES

/S/
Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/
Ameeta Parekh, Ph.D.

Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 21-149 (orig., 1 copy)
HFD-580 (DeGuia, Bennett, Slaughter)
HFD-870 (Kavanagh, Parekh)
Central Document Room (Barbara Murphy)

C:\REK\Reviews\NDA's\21-149 Ovidrel - Serono Labs\Labeling\6 Sponsor's Draft Labeling - 9-13-00 Reply\Ovidrel PI 9-13-00

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Last printed 09/14/00 11:14 AM

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Clinical Pharmacology & Biopharmaceutics
(HFD 860/870/880)
Tracking/Action Sheet for Formal/Informal Consults

By: Ronald E. Kavanagh, BS Pharm, PharmD, PhD

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified
IND/NDA submission

DATE: 11/23/99

IND No.: N/A
Serial No.:

NDA No.
21-149

Document ID:

DATE OF DOCUMENT
1/1/00

NAME OF DRUG

PRIORITY CONSIDERATION
S or P

Document Type and
Sequence No.:

Date of informal/Formal
Consult: 9/7/00

NAME OF THE SPONSOR: []

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS ASSIGNMENT

- | | | |
|--|--|--|
| ☐ PRE-IND | ☐ DISSOLUTION/IN-VITRO RELEASE | ☐ FINAL PRINTED LABELING |
| ☐ ANIMAL to HUMAN SCALING | ☐ BIOAVAILABILITY STUDIES | ☐ LABELING REVISION |
| ☐ IN-VITRO METABOLISM | ☐ IN-VIVO WAIVER REQUEST | ☐ CORRESPONDENCE |
| ☐ PROTOCOL | ☐ SUPAC RELATED | ☐ DRUG ADVERTISING |
| ☐ PHASE II PROTOCOL | ☐ CMC RELATED | ☐ ADVERSE REACTION REPORT |
| ☐ PHASE III PROTOCOL | ☐ PROGRESS REPORT | ☐ ANNUAL REPORTS |
| ☐ DOSING REGIMEN CONSULT | ☐ SCIENTIFIC INVESTIGATIONS | ☐ FAX SUBMISSION |
| ☐ PK/PD- POPPK ISSUES | ☐ MEETING PACKAGE (EOP2/Pre-
NDA/CMC/Pharmacometrics/Others) | ☒ OTHER (SPECIFY BELOW):
[NDA Review] |
| ☐ PHASE IV RELATED | | |

REVIEW ACTION

☐ NAI (No action indicated)

- | | | |
|---|---|---|
| ☐ E-mail comments to: | ☒ Oral communication with | ☒ Formal Review/Memo (attached) |
| ☐ Medical ☐ Chemist ☐ Pharm-Tox | Name: [Bennett] | ☐ See comments below |
| ☐ Micro ☐ Pharmacometrics ☐ Others | ☐ Comments communicated in | ☐ See submission cover letter |
| (Check as appropriate and attach e-mail) | meeting/Telecon. see meeting minutes | ☐ OTHER (SPECIFY BELOW): |
| | dated: [] | [] |

REVIEW COMMENT(S)

☒ NEED TO BE COMMUNICATED TO THE SPONSOR

☐ HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:

[]

SIGNATURE OF REVIEWER: _____

/S/

Date 9/7/00

SIGNATURE OF TEAM LEADER: See Attached Review

Date 9/9/00

CC.: See Attached Review

Project Manager: _____ Date _____

New Drug Application
Office of Clinical Pharmacology and Biopharmaceutics Review

Addendum I - Labeling

NDA:	21-149
Type of Submission:	NDA 1/S
Generic Name:	Recombinant Human Chorionic Gonadotropin r-hCG
Formulation(s); Strength(s); Route(s)	Injection (Freeze-dried) 250 µg / 1 ml Subcutaneous Injection
Brand Name:	Ovidrel®
Sponsor:	Serono Laboratories, Inc. Norwell, MA
Submission Date(s):	Latest Labeling Submission: August 14, 2000 Original NDA Submission: November 23, 1999
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. LABELING COMMENTS

This labeling review covers the sponsor's reply (submission date August 14, 2000) to the initial OCPB labeling comments made in the final review of this NDA submission and that were previously communicated to the sponsor.

Text with a single ~~strike-through~~ is to be deleted.

Underlined text is to be added, (except for section headings).

Text that is highlighted in the sponsor's reply to OCPB reviewer's initial response indicate additions made by the sponsor to the sponsor's initial proposal

Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments
Pharmacokinetics When given by intravenous administration, the pharmacokinetic profile of Ovidrel® followed a biexponential model. _____ linear over the range from 25 mcg to 1000 mcg. _____ _____ _____ _____ _____ Pharmacokinetic parameter estimates _____ following SC administration of Ovidrel® 250 mcg to females are presented in Table 1.	Pharmacokinetics When given by intravenous administration, the pharmacokinetic profile of Ovidrel® followed a biexponential model: _____ _____ and was linear over a range of 25 mcg to 1000 mcg. _____ _____ _____ _____ Pharmacokinetic parameter estimates _____ following SC administration of Ovidrel® 250 mcg to females are presented in Table 1.	Estimates of pharmacokinetic parameters and metrics have been limited to specific subsections for each metric, in order to avoid duplication and confusion.

Sponsor's Proposal Follows:

Table 1: Pharmacokinetic Parameters (mean $\pm$ SD) of hCG after Single-Dose Administration of Ovidrel® in Healthy Female Volunteers)

	Ovidrel® SC (250 mcg)
C_{max} (IU/L)	714 ± 44
t_{max} (h)*	24 (12-24)
AUC (h·IU/L)	7701 ± 2101
$t_{1/2}$ (h)	29 ± 6
F	0.4 ± 0.1

C_{max} : peak concentration (above baseline), t_{max} : time of C_{max} , AUC: total area under the curve, $t_{1/2}$: elimination half-life, F: bioavailability
 * median (range)

OCPB Reviewer's Response Follows:

Comment:

Table 1: Pharmacokinetic Parameters (mean $\pm$ SD) of hCG after Single-Dose Administration of Ovidrel® in Healthy Female Volunteers

	Ovidrel® SC (250 mcg)
C_{max} (IU/L)	121 ± 44
t_{max} (h)*	24 (12-24)
AUC (h·IU/L)	7701 ± 2101
$t_{1/2}$ (h)	29 ± 6
F	0.4 ± 0.1

C_{max} : peak concentration (above baseline), t_{max} : time of C_{max} , AUC: total area under the curve, $t_{1/2}$: elimination half-life, F: bioavailability
 * median (range)

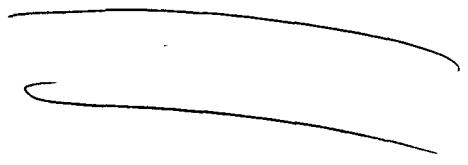
Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments
<u>Absorption</u> Following subcutaneous administration of Ovidrel®, maximum serum concentration is reached after approximately ~~12 to 24 hours~~ . The mean absolute bioavailability of Ovidrel® following a single subcutaneous injection to healthy female volunteers is about 40%.	Acceptable	
<u>Distribution</u> ~~Following intravenous administration of Ovidrel® to healthy down-regulated female volunteers, the serum profile of hCG is described by a two-compartment model with an initial half-life of 4.5 ± 0.5 hours. The steady state volume of distribution is 5.9 ± 1.0 L.~~	<u>Distribution</u> Following intravenous administration of 250 mcg Ovidrel® to healthy down-regulated female volunteers, the serum profile of hCG ~~is~~ described by a two-compartment model with an initial half-life of 4.5 ± 0.5 hours. The <u>volume of the central compartment is 3.0 ± 0.5 L and the steady state volume of distribution is 5.9 ± 1.0 L.</u>	• References to metrics referring to other than volumes of distribution have been removed, and/or moved to other sections. • Additional distribution data has been included

Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments
<u>Metabolism/Excretion</u> Following subcutaneous administration of Ovidrel®, ~~hCG~~ is eliminated from the body with a ~~mean~~ terminal half-life of _____ hours. One-tenth of the _____ dose is excreted in the urine.	<u>Metabolism/Excretion</u> Following subcutaneous administration of Ovidrel®, hCG is eliminated from the body with a mean terminal half-life of ~~_____~~ <u>29 ± 6</u> hours. After intravenous administration of 250 mcg to healthy down regulated females, the mean terminal half life is <u>26.5 ± 2.5</u> hours and the total body clearance is <u>0.29 ± 0.4 L/h.</u> One-tenth of the _____ dose is excreted in the urine.	• Elimination data from various subsections have been included in a single location. • Since drug would be <u>approvable as a single dose</u>
<u>Pharmacodynamics</u> ~~In~~ female subjects on oral contraception ~~after an initial latency period~~ Ovidrel® induced a clear increase in androstenedione serum levels ~~by 24 hours after dosing~~. Pharmacodynamic studies in both males and females determined that the ~~relationship of Ovidrel® pharmacokinetics to pharmacologic effect of Ovidrel® are complex and vary with the pharmacodynamic marker examined~~. In general pharmacologic effects are not	Acceptable.	

and

Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments
proportional to exposure and in some cases appear to be near maximal at a 250 mcg dose.		
Population pharmacokinetics and pharmacodynamic In ~~the~~ Ovidrel® ~~study~~ subcutaneously to trigger ovulation, the results of a population PK/PD analysis ~~showed~~ generally supported the data obtained in healthy subjects. Pharmacokinetic parameters for Ovidrel® include ~~the~~ median apparent clearance: 0.51 L/hr ~~and~~ and median apparent volume of distribution: ~~the~~	Population pharmacokinetics and pharmacodynamics In patients undergoing in vitro fertilization/embryo transfer given ~~the~~ Ovidrel® ~~study~~ subcutaneously to trigger ovulation, the results of a population PK/PD analysis ~~showed~~ generally supported the data obtained in healthy subjects. Pharmacokinetic parameters for Ovidrel® include median elimination half-life of 29.2 hours, ~~the~~ median apparent clearance: (Cl/F) of 0.51 L/hr ~~and~~ and median apparent volume of distribution: (V/F) of 21.4 L ~~the~~	• Edit section heading • Data more specific • ~~_____~~
Drug-Drug Interactions: No drug-drug interaction studies have been conducted. Administration of Ovidrel® may interfere with the interpretation of pregnancy tests. (see PRECAUTIONS.)	Acceptable	

Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments
DOSAGE AND ADMINISTRATION <i>For Subcutaneous Use Only</i> Infertile Women Undergoing Assisted Reproductive Technologies (ART)	DOSAGE AND ADMINISTRATION <i>For Subcutaneous Use Only</i> Infertile Women Undergoing Assisted Reproductive Technologies (ART)	
Ovidrel® 250 mcg one day following the last dose of the follicle stimulating agent. administration should be withheld in situations where there is an excessive ovarian response, as evidenced by clinically significant ovarian enlargement or excessive estradiol production.	Ovidrel® 250 mcg one day following the last dose of the follicle stimulating agent. <u>Ovidrel® should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography.</u> Administration should be withheld in situations where there is an excessive ovarian response, as evidenced by clinically significant ovarian enlargement or excessive estradiol production.	

Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments
Infertile Women Undergoing Ovulation Induction (OI)	Infertile Women Undergoing Ovulation Induction (OI)	
Ovidrel® should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. Ovidrel® 250 mcg should be administered one day following the last dose of the follicle stimulating agent. Ovidrel® administration should be withheld in situations where there is an excessive ovarian response, as evidenced by multiple follicular development, clinically significant ovarian enlargement or excessive estradiol production.	Ovidrel® should not be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. Ovidrel® 250 mcg should be administered one day following the last dose of the follicle stimulating agent. Ovidrel® administration should be withheld in situations where there is an excessive ovarian response, as evidenced by multiple follicular development, clinically significant ovarian enlargement or excessive estradiol production.	
Administration: 	Administration: 	

Sponsor's Reply to OCPB Reviewer's Initial Response	OCPB Reviewer's Response	Comments

II. SIGNATURES

/S/

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

9/7/00
Date

/S/

Ameeta Parekh, Ph.D.

Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

9/9/00
Date

CC: NDA 21-149 (orig., 1 copy)
HFD-580 (DeGuia, Bennett, Slaughter)
HFD-870 (Kavanagh, Parekh)
Central Document Room (Barbara Murphy)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults				
1: Ronald F. Kavanagh, BS Pharm, PharmD, PhD		To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission				
DATE: 9/7/00	IND No.: Serial No.:	NDA No. 21-149	Document ID:			
NAME OF DRUG [Ovidrel(r) r-hCG]		PRIORITY CONSIDERATION S	DATE OF DOCUMENT ~~4-1-00~~			
NAME OF THE SPONSOR: [Serono]		Document Type and Sequence No.:	Date of informal/Formal Consult: ~~4-1-00~~			
TYPE OF SUBMISSION CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS ASSIGNMENT						
<table style="width: 100%; border: none;"> <tr> <td style="vertical-align: top; width: 33%;"> ☐ PRE-IND ☐ ANIMAL to HUMAN SCALING ☐ IN-VITRO METABOLISM ☐ PROTOCOL ☐ PHASE II PROTOCOL ☐ PHASE III PROTOCOL ☐ DOSING REGIMEN CONSULT ☐ PK/PD- POPPK ISSUES ☐ PHASE IV RELATED </td> <td style="vertical-align: top; width: 33%;"> ☐ DISSOLUTION/IN-VITRO RELEASE ☐ BIOAVAILABILITY STUDIES ☐ IN-VIVO WAIVER REQUEST ☐ SUPAC RELATED ☐ CMC RELATED ☐ PROGRESS REPORT ☐ SCIENTIFIC INVESTIGATIONS ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) </td> <td style="vertical-align: top; width: 33%;"> ☐ FINAL PRINTED LABELING ☒ LABELING REVISION ☐ CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ ANNUAL REPORTS ☐ FAX SUBMISSION ☐ OTHER (SPECIFY BELOW): [] </td> </tr> </table>				☐ PRE-IND ☐ ANIMAL to HUMAN SCALING ☐ IN-VITRO METABOLISM ☐ PROTOCOL ☐ PHASE II PROTOCOL ☐ PHASE III PROTOCOL ☐ DOSING REGIMEN CONSULT ☐ PK/PD- POPPK ISSUES ☐ PHASE IV RELATED	☐ DISSOLUTION/IN-VITRO RELEASE ☐ BIOAVAILABILITY STUDIES ☐ IN-VIVO WAIVER REQUEST ☐ SUPAC RELATED ☐ CMC RELATED ☐ PROGRESS REPORT ☐ SCIENTIFIC INVESTIGATIONS ☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ FINAL PRINTED LABELING ☒ LABELING REVISION ☐ CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ ANNUAL REPORTS ☐ FAX SUBMISSION ☐ OTHER (SPECIFY BELOW): []
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REVIEW ACTION						
☐ NAI (No action indicated)						
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REVIEW COMMENT(S)						
☒ NEED TO BE COMMUNICATED TO THE SPONSOR ☐ HAVE BEEN COMMUNICATED TO THE SPONSOR						
COMMENTS/SPECIAL INSTRUCTIONS: []						
SIGNATURE OF REVIEWER: <u> / S / </u>		Date <u> 9/7/00 </u>				
SIGNATURE OF TEAM LEADER: <u> See Attached Review </u>		Date <u> 9/9/00 </u>				
CC.: See Attached Review		Project Manager: _____ Date _____				

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-149
Type of Submission:	NDA 1/S
Generic Name:	Recombinant Human Chorionic Gonadotropin r-hCG
Formulation(s);	Injection (Freeze-dried)
Strength(s);	250 µg / 1 ml
Route(s)	Subcutaneous Injection
Brand Name:	Ovidrel®
Sponsor:	Serono Laboratories, Inc. Norwell, MA
Submission Date(s):	November 23, 1999 April 7, 2000 May 17, 2000 (FAX) August 9, 2000 (FAX)
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. SYNOPSIS

What indication(s) is r-hCG being proposed for and how does this compare to the approved indications for u-hCG?

The proposed indication for r-hCG is as part of an Assisted Reproductive Technology (ART) program

Why develop r-hCG?

r-hCG is a replacement product for urinary hCG, which is sourced from pregnant women. Production of a recombinant product should result in a more reliable source of production.

A priori, do we expect any differences in the biological effects of these products?

Yes. The biologically sourced and recombinant products would be expected to differ in the major and minor species, their glycosylation, and their tertiary structures. These differences could in theory result in differences in biological effect and pharmacokinetics.

Are there any actual differences in pharmacokinetics between u-hCG and r-hCG?

Classical pharmacokinetic studies examining both intravenous administration (study 7012) and subcutaneous administration (7014) demonstrated increased clearance with r-hCG compared to u-hCG.

In contrast, in a population pharmacokinetic study of women undergoing infertility treatment (GF 7648), a larger AUC was observed with r-hCG compared with u-hCG. This difference is in the opposite direction from that observed in studies 7012 and 7014. This higher AUC with r-hCG is due to a combination of lower V/F (79.3%) and Cl/F (82.3). Consequently, it could be due to differences in F. Alternatively, since the actual dose administered was not verified, the difference could be due to differences in dose and thus whether the difference is real or not is debatable. In addition, the sponsor claims that the findings are opposite to those observed in the US based phase III study (GF 7927), however no data was presented.

Are there any significant issues in the recommended dosage and administration for the proposed r-hCG products compared with u-hCG?

u-hCG and r-hCG are both lyophilized powders for reconstitution. However, the packaging for u-hCG includes 5000 or 10,000 IU in a 10 ml vial, to be reconstituted with _____ water for injection (_____. Dosages of 5000 or 10,000 units are recommended. The route of administration is not specified in the labeling for u-hCG, although typically administration is IM or SC, which would suggest reconstitution with _____ 5000 units, for a final concentration of ≤ 5000 IU/ml.

The proposed packaging for r-hCG contains 285 _____ per vial (nominally equivalent to 5700 or 11500 units / vial although actual activities varied) to be reconstituted with 1 ml of sterile water for injection. Administration is subcutaneous. Although the volume to be administered is not explicitly stated in the labeling or in clinical trials, the entire contents of the vial is to be administered. Claims by the sponsor in the NDA and in the labeling indicate that the dosage delivered is 250 mcg (_____) (i.e. 5000 or 10000 IU). Calculations provided by the sponsor indicate the actual dose delivered, especially when considering actual reconstitution and administration by patients may be slightly less. However, the variation should be within acceptable limits.

The administration instructions in the phase III trial examined (GF 9073) are unclear and are not accurately reflected in the proposed labeling. In this study, r-hCG was provided as 285 mcg/vial, and was reconstituted with 1 ml, although the protocol states the amount of drug as 250 mcg per vial. In addition, the injection site was not defined.

Are the clinical trial drug product and the to-be-marketed drug product the same?

Except for different production sites, there are no significant differences in manufacturing between the clinical trial drug product and the to-be-marketed drug product. Thus, no differences in the products are expected.

Are there any differences between the clinical trial batches and the to be marketed formulations in terms of activity?

As measured by a bioassay, the clinical trial batches varied widely in activity between batches. In addition, the dose administered as determined by the bioassay was also highly variable. The to-be marketed formulation is to be filled based upon mass and thus differences in activity between batches could occur if there are major differences in minor species, glycosylation, etc.. However, the chemists claim that the differences between the clinical trial batches should be minor and that filling based upon mass is acceptable. Based upon the highly variable activity measured within batches across time from the stability studies, it appears that the wide measurements of activity in the clinical trial batches may be due to assay variability.

Are the pharmacokinetics of r-hCG linear with dose?

The pharmacokinetics of r-hCG are linear over a dosage range of 500 to 44,000 IU after IV administration. No similar studies were performed with IM or SC administration, although other studies suggest that route of administration can effect bioavailability and possibly first pass effect.

What differences are there in r-hCG pharmacokinetics with route of administration?

In men, bioavailability is 28.8% lower after SC administration compared with IM administration, although absorption is faster after SC administration.

Are there any gender-based differences in the pharmacokinetics of r-hCG?

Yes, the higher bioavailability after IM administration compared with SC administration is completely due to higher bioavailability in men after IM administration. Women have similar bioavailabilities after IM and SC administration. However, the bioavailability after SC administration is similar for men and women.

Are the pharmacokinetics of r-hCG time invariant?

Multiple dose pharmacokinetics were conducted in men for up to 5 doses at 48 hour intervals. This is an insufficient duration to assess time invariance, although there does appear to be changes in the pharmacodynamic effects on biomarkers over this time span. Even if there is time variance, since single doses of hCG would be given to women at monthly intervals, time invariance would not be a clinical issue. In males, a new equilibrium would eventually be reached and time invariance should not be a concern; since dose is titrated to clinical effect over long periods.

Is there any information on pharmacokinetics in special populations?

No information was provided on race, or other special populations such as renal or hepatic insufficiency. However, renal clearance data suggests that this is a minor elimination pathway accounting for approximately 12% of total body clearance.

Are there any differences in pharmacokinetics when data is analyzed utilizing the immunoassay and the bioassay?

When total hCG is measured there are differences in calculated pharmacokinetic metrics when the different assay methods are used. In one case, the steady-state AUC is much lower than the single dose AUC with the bioassay, thus indicating possible induction or decreased bioavailability over time. In the other case, there is a greater degree of bioavailability with the bioassay upon single dose administration. However, in virtually every subject the dose administered is lower when assessed by bioassay than when assessed by immunoassay. This in combination with the higher measured bioavailability, indicate complex differences in pharmacokinetics between different routes of administration and probably with drug source. One possible explanation is a difference in formation of an active metabolite on first-pass that is not detected by the immunoassay, although this hypothesis cannot be confirmed with the current data and assay methods. Since, most pharmacokinetic information was derived with the immunoassay, data based upon the immunoassay should be used for labeling purposes.

Are the phase I liquid formulation and the phase III freeze-dried formulations of r-hCG bioequivalent?

When data from both males and females are analyzed, the two formulations meet bioequivalence criteria for dose normalized C_{max} and AUC. When data is analyzed separately by gender, females (n=12) fail to meet bioequivalence criteria for C_{max}, [ratio of liquid phase I to freeze-dried phase III formulation (90% CI); 0.83 (0.74, 0.92)]. Apparent clearance also failed to meet bioequivalence criteria for C_{max}, [ratio of liquid phase I to freeze-dried phase III formulation (90% CI); 1.17 (1.08, 1.27)]. Since the two formulations were prepared from the same batch of drug substance and the only difference in preparation was the lyophilization step, it's possible that the difference could be spurious. In any event, a true difference should not be clinically significant.

Do the 250 mcg and 500 mcg doses of r-hCG give comparable bioavailability when adjusted for dose?

Yes.

What are the results of the pharmacokinetic/pharmacodynamic modeling?

PK/PD relationships for several biomarkers (testosterone, inhibin, and estradiol in men; and androstenedione and testosterone in women) were examined after single IV, IM and SC doses and over 5 SC doses in hormonally down-regulated healthy male and female volunteers. The PK/PD relationships were very complex and appeared to change over time. However, it appears that a r-hCG dose of 5000 IU is at or near the maximal effect for the biomarkers studied. Consequently, this data tends to support a clinical dose of 250 mcg r-hCG (nominally 5000 IU) for induction of ovulation.

What are the clinical implications of the pharmacokinetic and pharmacodynamic observations with r-hCG?

There are likely no clinical consequences due to the differences observed in the pharmacokinetics and pharmacodynamics of r-hCG; since in women, the drug is dosed as a single dose at a dosage that is likely at or near maximal efficacy.

II. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA #21-149 submitted November 23, 1999. The overall Human Pharmacokinetic Section is acceptable to OCPB. Some labeling changes have been negotiated with the sponsor and have been incorporated into the package insert as appropriate. Current labeling recommendations are included in Section X Labeling Comments on page 49). Additional changes to labeling, e.g. sponsor acceptance or additional negotiated labeling will be addressed in addendum(a) to this review as appropriate.

APPEARS THIS WAY
ON ORIGINAL

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II. RECOMMENDATION	4
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Table 1 Pharmacokinetic, Pharmacodynamic, Biopharmaceutic and Clinical Pharmacology Studies in NDA 21-149 for Ovidrel® (r-hCG)

Study Number	Study Title
GF 7012	A Phase I Study to Assess the Pharmacokinetics of Recombinant-Human Chorionic Gonadotrophin After Single IV Administration Increasing Doses, Compared to a Single IV Injection of Urinary Human Chorionic Gonadotrophin (Profasi®) in 12 Healthy Volunteers
GF 7013	A Phase I Study to Assess the Pharmacokinetics, Pharmacodynamics and the Bioavailability of Recombinant-Human Chorionic Gonadotrophin (r-hCG) After Single IV, IM, SC and Repeated SC Administration of 2500 IU in 12 Healthy Volunteers
GF 7014	A Phase I Study to Assess the Bioequivalence of a Liquid and a Freeze-Dried Formulation of Recombinant-Human Chorionic Gonadotrophin (r-hCG) After Single SC Administration of 250 µg, and to Compare Their Pharmacokinetics with Those of Urinary Human Chorionic Gonadotrophin (Profasi®) Following a Corresponding Single 5000 IU SC Injection
GF 8927	The origin of the β core molecule of human chorionic Gonadotropin (β-core hCG)
GF 6136	<i>This protocol was noted on page 009 of volume 37. It was described as a phase I clinical study in healthy female volunteers whose endogenous LH is suppressed by GnRH agonist. No other information on this protocol has been found in section 6 of NDA 21-149.</i>
IMP21443	An Open, Randomized, 2 Way Crossover Study in Healthy Male and Female Volunteers to Compare the Bioavailability of Ovidrel® Given as 1ml of 500µg/ml from the 500µg Strength Vial with 1ml of 500µg/ml from the 250µg Strength Vial
GF 7648	Population analysis of pharmacokinetic and pharmacodynamic data obtained during a phase III, double-blind, double-dummy, randomized, multicentre study to compare the safety and efficacy of recombinant human Chorionic Gonadotrophin (Ovidrel®) with that of urinary human Chorionic Gonadotrophin (Profasi®) for inducing final follicular maturation and early luteinisation in women undergoing superovulation with recombinant human Follicle Stimulating Hormone (Gonal-F®) prior to IVF/ET
GF 7927	<i>A population analysis of the US based phase III study. This data was not reported. The results were described as differing from GF 7648 in the population analysis study report of GF 7648.</i>

Table 2: Partial Demographics from Selected Clinical Pharmacology Studies

Protocol No. Study Start Dates	Phase/Completion Status	Study Location	Study Design	Treatment Doses	No. Subjects Entered	No. Subjects Each Treatment ("total, all treatments)	Age Range (years) ("from protocol)	M/F W/B/O	Duration of Treatment	Location of Report (Vol./Pg.)
Pharmacokinetic, Pharmacodynamic, Bioavailability										
7012 Feb 1994	Phase I Completed	UK	OL, partially randomized, dose-escalating, comparative	500, 5,000, 20,000 IU r-hCG IV bolus 5,000 IU Profasi®, IV bolus	12	12**	22-37	6/6 NA	4 single doses separated by 2 weeks	Vol.: 32 Page: 001
7013 Feb 1994	Phase I Completed	UK	OL, partially randomized, cross-over, stratified by sex, comparative	2,500 IU r-hCG IV, IM & SC 2,500 IU r-hCG, SC QOD	12	12**	19-37	6/6 NA	3 single doses separated by 2 weeks; QOD x 9 days (5 doses)	Vol.: 33 Page: 001
7014 Jul 1994	Phase I Completed	UK	SB, randomized, three-way, cross over, stratified by sex	5,000 IU r-hCG, SC 5,000 IU Profasi®, SC	24	24**	20-38	12/12 NA	3 single doses separated by 3 weeks	Vol.: 35 Page: 001
8927 Jul 1997	Phase I Completed	Australia	OL	44,000 IU r-hCG, IV bolus over 3 min	6	6	17-45	0/6 NA	single dose	Vol.: 35 Page: 476

B = Black; BIW = Two times per week; DB = Double Blind; F = Female; IM = Intramuscular; IU = International Unit; IV = Intravenous; M = Male; mcg = Microgram; NA = Not Available; OL = Open-Label; O = Other; PC = Placebo Controlled; SB = Single Blind; SC = Subcutaneous; TIW = Three times per week; W = White

1 IU/L u-hCG = 0.05 mcg/L r-hCG

III. INTRODUCTION

A. Background Information

For additional background information on hCG see APPENDIX 1 - OVERVIEW OF HUMAN CHORIONIC GONADOTROPIN.

B. Rationale for Development of r-hCG

Recombinant-human chorionic gonadotropin (r-hCG; Ovidrel®) is being developed as a pharmaceutical product to replace urinary-human chorionic gonadotropin (u-hCG; Profasi®).

The production method of r-hCG provides a manufacturing process that is no longer dependent on urine collection and extraction. Consequently, product availability may become less of an issue, especially if the use of hCG in anovulatory/infertile women continues to increase.

C. Sourcing and Availability of hCG

1. u-hCG

Urinary hCG is purified from the urine of pregnant women and is currently available from Serono Laboratories, Inc. under the tradename Profasi®.

2. r-hCG

Recombinant hCG is produced by genetically engineered chinese hamster ovary cells cultured in _____

is the subject of this NDA from Serono Laboratories, Inc. and its' proposed tradename is Ovidrel®. r-hCG

D. Clinical Use of u-hCG

According to the sponsor, in clinical practice hCG is administered according to the following dose ranges:

N.B. These clinical uses and dosages are not the same as the approved indications for u-hCG or the proposed indications or r-hCG. For r-hCG only the underlined use is similar to what is proposed for approval.

E. Indications (Approved for u-hCG and Proposed for r-hCG)

Table 3 compares the approved indications for u-hCG (Profasi®) with the proposed indications for r-hCG (Ovidrel®).

Treatment of prepubertal cryptorchidism and hypogonadotropic hypogonadism in males are both approved for u-hCG, however, neither indication is being sought for the replacement product r-hCG.

Although used in clinical practice for luteal phase support in females, this is not an approved indication for u-hCG. Neither is this being sought as an indication for r-hCG (see Table 3).

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G. Development Issues

Due to the variations in amino acid sequence, glycosylation and protein folding the actual chemical composition and tertiary structure of hCG can vary. (See APPENDIX 2 - CHEMISTRY for additional information on the chemistry of r-hCG and how it compares to u-hCG). Thus, *a priori* we would expect that u-hCG and r-hCG, and their various subspecies, could have varying receptor binding and thus varying pharmacologic potency. In addition, there could be differences in pharmacokinetics. The net effect could thus be differences in biological and clinical effects.

Consequently, the development program compared the *in vitro* pharmacodynamics and the *in vivo* pharmacokinetics and pharmacodynamics of u-hCG and r-hCG as well as the clinical efficacy and safety of r-hCG.

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IV. CHEMISTRY

A. MANUFACTURING SITES

1. Investigational Batches

Based upon information that was provided for investigational batches, it appears that drug substance and drug product were produced at the following sites:

Drug Substance

Laboratoires Serono S.A (LSA)
Aubonne, Switzerland

Drug Product

Instituto de Ricerca Cesare Serono, S.p.A. (IRCS)
Via Valle Caia 22
00040 Ardea
Rome, Italy

2. Commercial Batches

The manufacturing sites listed for the commercial product differs from the sites used for the investigational batches.

The proposed commercial manufacturing sites are listed below and the information was found on pages 111 & 131 of volume 2.2.

All manufacturing Operations including primary packaging are performed by:

Industria Farmaceutica Serono S.p.A.
Zona Industriale di Modugno
Bari, Italy

Serono Laboratories Inc.
76 Pacella Park Drive
Randolph, Mass 02386

No bridging studies were performed between the investigational and commercial batches.

Discussions with the chemistry reviewers indicate that there should not be major differences in the final to-be-marketed product and the phase III clinical trial product. Since, this is a parenteral formulation bridging studies generally would be not needed and any pharmacokinetic differences would likely to be due to lot to lot variation. In addition, it's unlikely such differences would be clinically meaningful if they occurred with the to-be-marketed product.

B. Qualitative-Quantitative Composition

1. Clinical Trial Formulations

A summary of the formulations used in the clinical trials is included in Table 5.

Table 5 Drug Formulations Used in Phase 1 and Phase 3 Studies

Study reference	Study Description	Batch N°	Production Site	Drug name	Formulation	Nominal Amount per Volume	Measured Amount per Volume
Phase I Studies: Liquid Formulation							
Study 7012	SD IV BE; r-hCG vs. u-hCG	001	IRCS	r-hCG (liquid)	0.5 mL contains		
Study 7013	r-hCG PK & PK/PD vs. Route	001	IRCS		Choriogonadotropin alfa 250 mcg	250 mcg/0.5 ml	
Study 7014	3-way BE Iyo vs. liq r-hCG vs. u-hCG	002	IRCS			5000 IU/0.5 ml	
Study 8927	IV; Renal and NR CI and metabolism	95CA04	IRCS	liquid			
Phase I Studies: Freeze-dried Formulation 250 µg							
Study 7014	3-way BE Iyo vs. liq r-hCG vs. u-hCG	002	IRCS	r-hCG (freeze-dried)	One vial contains:		
Study 8927	IV; Renal and NR CI and metabolism	95CA04			Choriogonadotropin alfa 285 mcg/vial	250 mcg	
21443	BE 250 mcg vs. 500 mcg Vial	98AA02			Sucrose 30.0 mg		
					O-Phosphoric Acid 0.98 mg		
					Sodium Hydroxide q.s. to pH 7.0		
					Solvent: Water for Injection		
Phase I Studies: Freeze-dried Formulation 500 µg							
21443	BE 250 mcg vs. 500 mcg Vial	99AH02		r-hCG (freeze-dried)	One vial contains:		
					Choriogonadotropin alfa 500 mcg		
					Sucrose 30.0 mg		
					O-Phosphoric Acid 0.98 mg		
					Sodium Hydroxide q.s. to pH 7.0		
					Solvent: Water for Injection		
Phase 3 Studies: Freeze-dried Formulation							
Study 7927	US Phase III Study (No PK)	95CA04 95CA05 95CA10		r-hCG (freeze-dried)	One vial contains:		
					Choriogonadotropin alfa 285 mcg/vial	250 mcg	
					Sucrose 30.0 mg		
					O-Phosphoric Acid 0.98 mg		
					Sodium Hydroxide q.s. to pH 7.0		
					Solvent: Water for Injection		
Study 7648	EU Phase III and Pop PK	RHCG002 95CA04 95CA05					

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information that is not
disclosable.

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For the 250 mcg vials measured activity in commercial scale batches ranged from _____ to _____ IU/ml, i.e. _____ to _____ of intended. In pilot scale batches activity ranged from _____ to _____ IU/ml, i.e. _____ to _____ of intended.

Based upon the wide variability in activity observed during the stability study within the same batch, it's likely that the wide variability in activity between batches is due to variability in the analysis. How much true variability there is between batches is currently impossible for this reviewer to determine based upon the information available.

2. To Be Marketed Formulations and Primary Packaging

The qualitative-quantitative composition of the proposed to-be-marketed drug products (250 µg _____ are listed on pages 111 and 131 of volume 2.2 of the NDA and in Table 7. These products are lyophilized and are reconstituted with 1 ml of sterile water for injection.

Primary packaging consists of consists of one _____

Table 7 Qualitative-Quantitative Composition of To-Be-Marketed Products

Nominal Vial Size	Qualitative Composition	Claimed Quantitative Amount per Vial	Claimed Amount per 1 ml post Reconstitution
250 µg	Choriogonadotropin alfa	285 mcg/vial	250 mcg
	Sucrose	30.0 mg	_____
	O-Phosphoric Acid	0.98 mg	_____
	Sodium Hydroxide	q.s. to pH 7.0	_____
	Reconstitution Solvent: Sterile Water for Injection	_____	_____

C. Comparison of To-be-marketed and Clinical Trial Batches

1. Qualitative-Quantitative Composition

The to-be-marketed qualitative-quantitative composition is the same as that used in pharmacokinetic studies 7014, 8927 and 21344 and in both Phase III trials (Studies 7927 and 7648). (See Table 1)

2. Manufacturing Site - Finished Product

It appears that the manufacturing site for the finished product used in PK studies 7012, 7013, and 7014 are different from the site for the to-be-marketed product. For the other pharmacokinetic and clinical trials, there's no clear accounting of the finished product manufacturing sites.

3. Manufacturing Site - Bulk Drug Substance

Limited information was provided on the bulk drug substance. The information available indicates that the bulk substance used in most clinical trials were coded S04 through S07 and that these batches were all manufactured at IRCS/LSA and not at the commercial manufacturing site. Although for drug product lot 99AH02 that was used in study 21443 drug substance lot BCEA 9902 was used. The manufacturing site of this batch is not mentioned.

4. Amount, Final Concentration, and Volume Administered

As seen by the limited information in Table 5 there may also be slight differences in amount of drug substance in different finished product batches that were used in different studies. In addition, the final volume and concentration injected may have differed between studies, and this could be a significant factor with a drug given subcutaneously (See Table 6).

5. Batch Size

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7. Conclusion

In conclusion, there are several reasons to suspect that the clinical trial batches may not be representative of the commercial batches. However, based on discussions with the chemistry reviewers there should not be major differences between the clinical trial batches and the final to-be-marketed product. Since this is a parenteral formulation bridging studies are not needed and any differences in pharmacokinetics would likely be due to lot to lot variation.

V. PHARMACOLOGY

A. Units

The claimed activity is _____ . Not justification was provided for this conversion factor.

B. Activity of Metabolites

_____ as potent as hCG. See reference citation in study 7014.

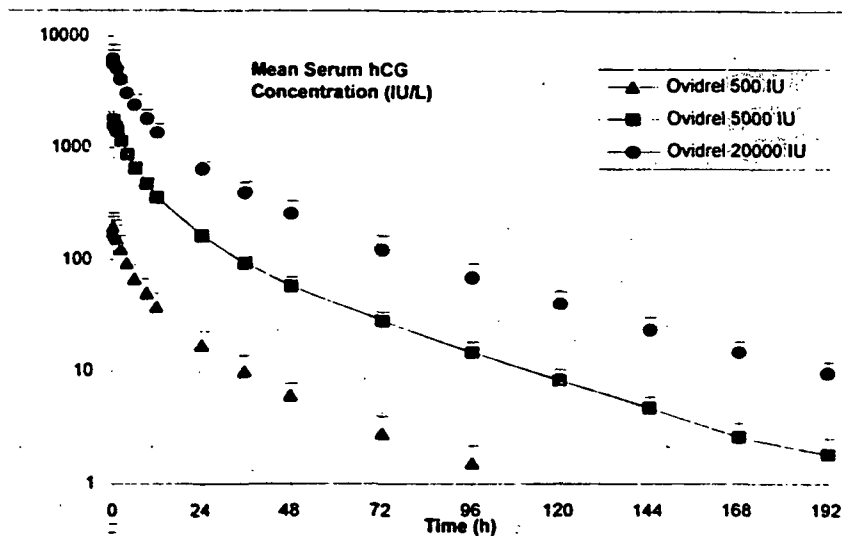
VI. PHARMACOKINETICS

A. Dose Linearity After Intravenous Administration

Ovidrel® exhibits linear pharmacokinetics after IV administration over the dose range of 500 IU to 44,000 IU (studies 7012 and 8927).

After intravenous administration Ovidrel® demonstrated a biexponential decline in the concentration vs. time profile (see Figure 1; figure from study 7012).

Figure 1 Mean ($\pm$ sd) concentration-time data following IV administration of Ovidrel® 500, 5000 and 20000 IU



Pharmacokinetic metrics after intravenous administration as provided by the sponsor are shown in Table 11. In calculating these values, data from two subjects at the 500 IU dose were excluded due to being outliers (See Figure 2).

Table 11 Pharmacokinetic Metrics of Ovidrel® After Intravenous Administration

		500 IU Ovidrel®	5000 IU Ovidrel®	20000 IU Ovidrel®
Dose	IU ^a	490 ± 146	5130 ± 166	22206 ± 906
	µg	25.6 ± 7.7	270 ± 9	1169 ± 46
C ₁	(IU·L ⁻¹)	156 ± 34	1399 ± 317	5349 ± 886
	(µg·L ⁻¹)	8.2 ± 1.8	75.4 ± 16.3	290 ± 38
λ ₁	(h ⁻¹)	0.180 ± 0.026	0.151 ± 0.023	0.141 ± 0.0189
t _{1/2} (1)	(h)	3.9 ± 0.7	4.7 ± 0.8	5.0 ± 0.7
C _z	(IU·L ⁻¹)	32.0 ± 8.1	192 ± 60	694 ± 183
	(µg·L ⁻¹)	1.7 ± 0.4	10.5 ± 2.9	38.2 ± 8.3
λ _z	(h ⁻¹)	0.031 ± 0.005	0.025 ± 0.003	0.023 ± 0.002
t _{1/2}	(h)	23 ± 4	28 ± 3	30 ± 2
AUC	(IU·h·L ⁻¹)	1904 ± 338	16804 ± 2356	67814 ± 8530
	(µg·h·L ⁻¹)	100 ± 18	899 ± 118	3657 ± 352
CL	(L·h ⁻¹)	0.28 ± 0.05	0.31 ± 0.04	0.33 ± 0.04
Cl _r	(L·h ⁻¹)	0.034 ± 0.010	0.028 ± 0.012	0.030 ± 0.008
fe	(%)	11.9 ± 2.6	9.1 ± 3.4	9.0 ± 2.5
MRT	(h)	20 ± 3	22 ± 3	23 ± 2
V _c	(L)	2.9 ± 0.6	3.4 ± 0.7	3.8 ± 0.7
V _{ss}	(L)	5.7 ± 1.1	6.7 ± 1.2	7.7 ± 1.4

a Dose measured by immunoassay

B. Single Dose Pharmacokinetics - Effect of Route of Administration

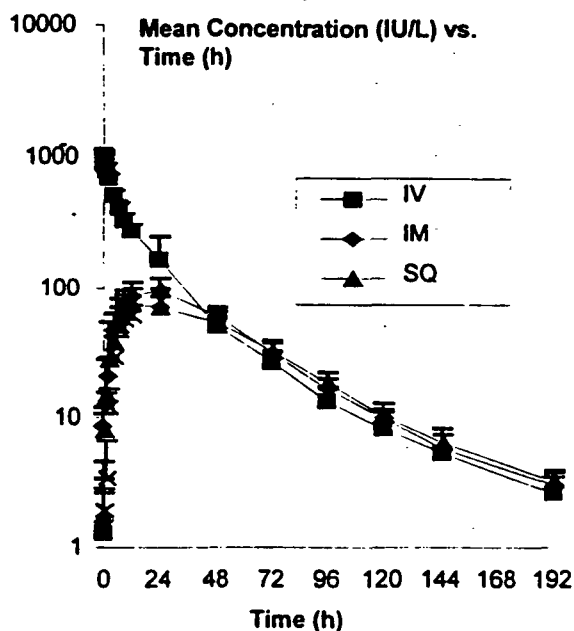
Study 7013 compared the pharmacokinetics of r-hCG after single dose administration by the IV, IM, SC routes, and after multiple subcutaneous injections. The extent of absorption is lower and the rate more rapid after subcutaneous injection. There is also a gender difference when administered by IM injection, but not after subcutaneous injection. This gender difference also results in the net difference in pharmacokinetics between IM and SC injection.

1. Serum Concentration vs. Time Profile

When Ovidrel® 2500 IU (r-hCG) is administered by intravenous injection a biphasic serum concentration vs. time profile is observed, with the first phase presumably due to distribution. When administered by the subcutaneous or intramuscular routes a biphasic serum concentration vs. time profile is also observed

(See Figure 3). The distribution phase is not distinguishable after IM or SC administration due to the similar rate of absorption and the rate of distribution.

Figure 3 Comparison of Mean ($\pm$ sd) r-hCG Serum Concentration vs. Time Profiles when Administered by Different Routes as Assessed by Immunoassay



2. Single Dose Pharmacokinetic Metrics by Route of Administration

As shown in Table 12 there are slight differences in r-hCG pharmacokinetic metrics when administered by various routes.

As expected, C_{max} is much higher after IV administration due to rapid systemic input. The AUC is also much higher due to a lack of, or diminished first pass effect. What is surprising is the longer and more variable terminal half-life after IV administration compared to IM or SC administration.

Comparison of pharmacokinetic metrics after IM and SC administration reveals a slightly slower absorption after SC administration, although the rate of absorption after IM administration is more variable. What is most striking is the 19.2% lower absolute bioavailability after SC administration compared with absolute bioavailability after IM administration. This is also reflected in the 12% lower AUC and 19.7% lower dose normalized AUC seen after SC administration compared with IM administration. A lower C_{max} and dose normalized C_{max} is also seen after SC administration compared with IM administration. This is likely due decreased bioavailability, since absorption is more rapid after SC administration.

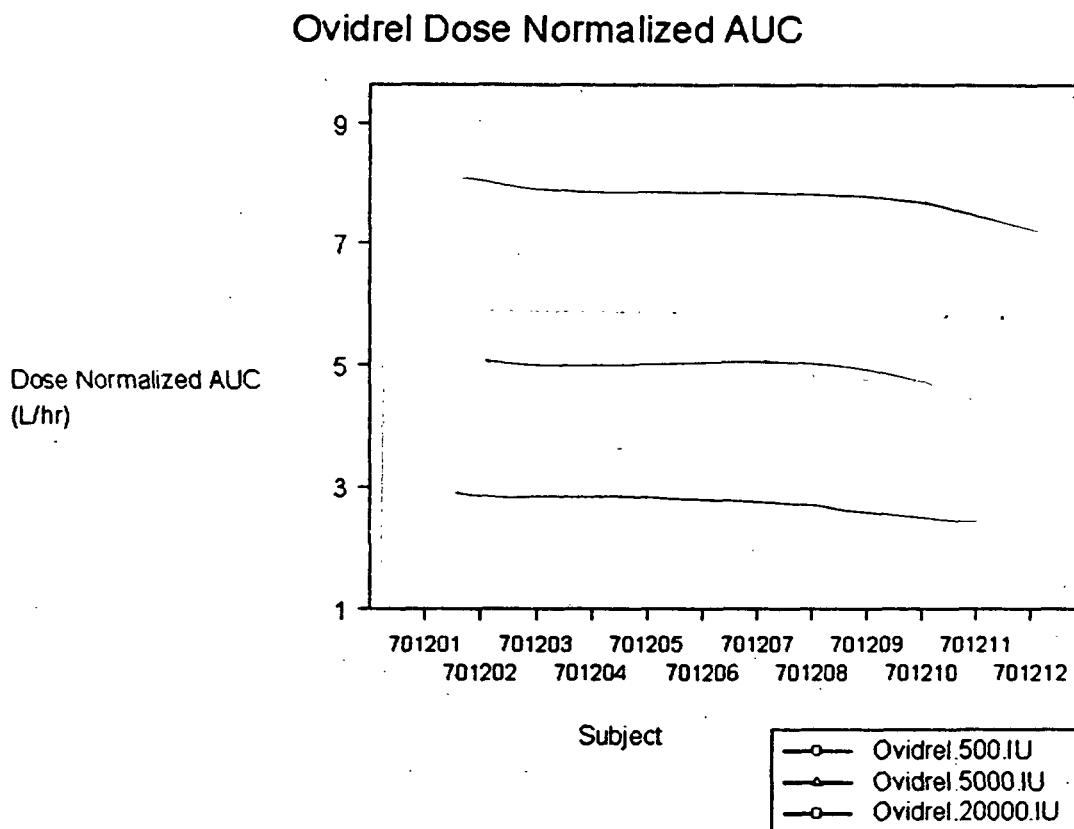
In study 7012 no differences were found between dose normalized AUC's from dosage levels of 500, 5000 and 20,000 IU, $p = 0.1$ by ANOVA on log transformed data (See Table 10; data from study 7012).

Table 10 Dose Normalized AUCs for Ovidrel® after Intravenous Administration by Noncompartmental Modeling

	500 IU Ovidrel®	5000 IU Ovidrel®	20000 IU Ovidrel®
DN AUC (h·L ⁻¹)	3.60 ± 0.80	3.28 ± 0.45	3.05 ± 0.38

This is demonstrated graphically by the similar dose normalized AUC's between doses both within and between subjects (See Figure 2).

Figure 2 Ovidrel® Dose Normalized AUC



This is not conclusive evidence of dose linearity, although it is strongly suggestive. This reviewer did not confirm dose linearity as the data was not in a format allowing easy manipulation. It should be noted that data from the 2 outliers at the 500 IU dose level were excluded from the analysis. This was done since there was a suggestion that the calculation of the dose administered may have been spuriously low in these two subjects. In spite of this, it's likely that the pharmacokinetics are indeed linear.

Additional evidence of linear pharmacokinetics is provided by study 8927. In this study a 44,000 IU dose was administered IV over 3 minutes. Reported pharmacokinetic metrics from study 8927 are virtually identical to the metrics reported for study 7012 (See section VI.F for a comparison).

Table 12 Mean ($\pm$ sd) Single Dose Pharmacokinetic Metrics for Different Routes of Administration as Determined from Immunoassay Data

Parameter	Route of Administration		
	IV	IM	SC
C_{max} (IU·L ⁻¹)	1008 $\pm$ 107	94 $\pm$ 23	79 $\pm$ 18
t_{max}^* (h)	—	24 (12-24)	18 (12-24)
C_{maxDN} (L ⁻¹)	0.40 $\pm$ 0.045	0.038 $\pm$ 0.01	0.030 $\pm$ 0.007
AUC (IU·h·L ⁻¹)	12917 $\pm$ 1831	5801 $\pm$ 951	5123 $\pm$ 958
AUC _{DN} (h·L ⁻¹)	5.13 $\pm$ 0.81	2.36 $\pm$ 0.49	1.92 $\pm$ 0.39
λ_1 (h ⁻¹)	0.244 $\pm$ 0.193	—	—
$t_{(1)/2}$ (h)	4.4 $\pm$ 2.4	—	—
λ_2 (h ⁻¹)	0.026 $\pm$ 0.009	0.028 $\pm$ 0.0089	0.0262 $\pm$ 0.0062
$t_{1/2}$ (h)	29.2 $\pm$ 9.7	27 $\pm$ 8	28 $\pm$ 6
CL (L·h ⁻¹)	0.2 $\pm$ 0.03	—	—
MRT (h)	27 $\pm$ 5	—	—
MAT (h)	—	22 $\pm$ 13	26 $\pm$ 10
k_a (h ⁻¹)	—	0.089 $\pm$ 0.026	0.114 $\pm$ 0.070
$t_{(a)/2}$ (h)	—	8.4 $\pm$ 2.3	8.9 $\pm$ 5.7
V_c (L)	2.7 $\pm$ 0.4	—	—
V_{ss} (L)	5.3 $\pm$ 1.3	—	—
F	—	0.47 $\pm$ 0.12	0.38 $\pm$ 0.1

* Median and range values determined by noncompartmental analysis whenever possible

3. Gender Differences by Route of Administration

As noted earlier absolute bioavailability is higher after IM administration compared to subcutaneous administration. Upon further examination, it becomes apparent that the higher bioavailability after IM administration is due to greater bioavailability in males (See Section VI.D.2 for a more complete discussion)

C. Multiple Dose Pharmacokinetics - Subcutaneous Administration

r-hCG multiple dose pharmacokinetic metrics were studied in 6 men and 6 women in study 7013. Comparison of pharmacokinetic metrics after the first and fourth doses of r-hCG 2500 IU SC reveal an accumulation of r-hCG and a shorter time to t_{max} after 4 doses (See Table 13 and Figure 4). For comparison, data is also shown for r-hCG administered SC on a single occasion to the same group of subjects.

The degree of accumulation over the first four SC doses given at 48 hour intervals as calculated by the dose normalized AUC accumulation ratio is 1.69 ± 0.62 (See Table 13).

Another reflection of the degree of accumulation can be obtained by comparing the C_{max} 's. This gives an approximate accumulation ratio

The dosage interval AUC at steady-state ($AUC_{192-240}$) is similar to the total AUC after a single dose ($AUC_{0-\infty}$). This also holds for the dose normalized values, indicating time invariant pharmacokinetics over 4 doses. Ideally, time invariance should have been evaluated over a longer time frame since physiologic changes can take longer than 8 days to occur and to reach a new equilibrium.

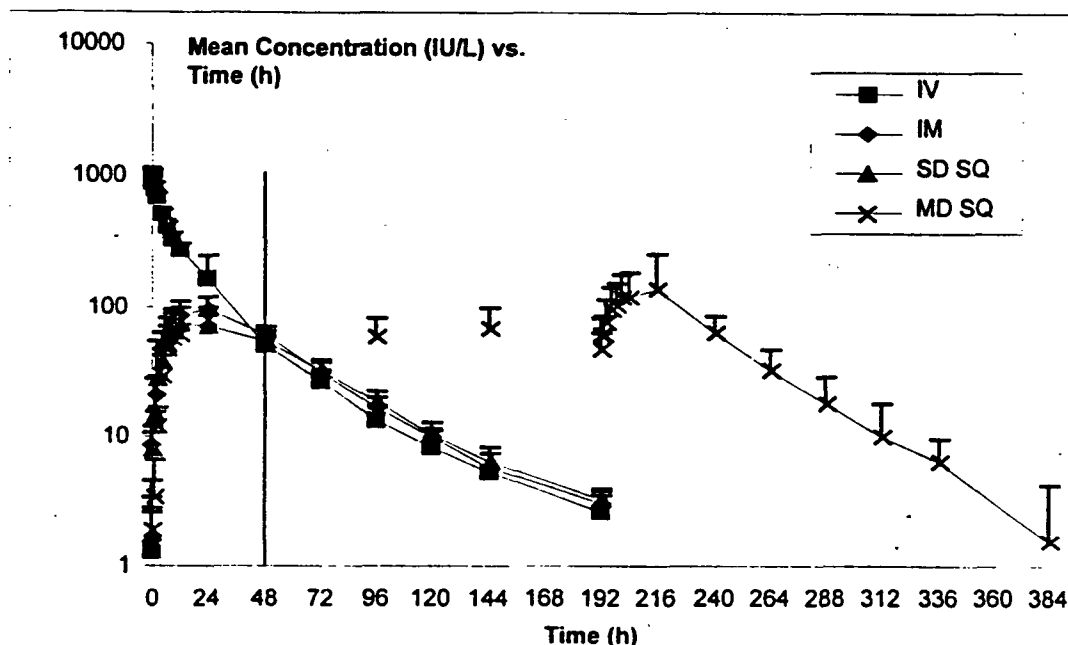
Since r-hCG would only be used as a single dose in women for infertility, time variant pharmacokinetics would not be a clinical issue in this population. For men who would be receiving this hormone chronically it's more of a consideration. However, since a new equilibrium would be reached eventually, the pharmacologic effects are dependent upon chronic administration, and dose is titrated to effect, time variant kinetics should be of little clinical consequence even if it should occur.

Table 13 Comparison of Single and Multiple Dose Pharmacokinetic Metrics after Subcutaneous Administration

Parameter	Subcutaneous Administration		
	Single Dose	Multiple Dose Administration	
		First Dose 0 - 48 hours	Fourth Dose 192 - 240 hours
C_{max} (IU·L ⁻¹)	79 ± 18	81 ± 18	154 ± 117
t_{max}^* (h)	18 ± —	24 ± —	12 ± —
C_{maxDN} (L ⁻¹)	0.030 ± 0.007	0.033 ± 0.008	0.063 ± 0.047
AUC (IU·h·L ⁻¹)	5123 ± 958	2850 ± 676	5077 ± 3140
AUC_{DN} (h·L ⁻¹)	1.92 ± 0.39	1.17 ± 0.28	2.08 ± 1.26
λ_z (h ⁻¹)	0.0262 ± 0.0062	—	0.0222 ± 0.003
$t_{1/2}$ (h)	28 ± 6	—	32 ± 5
MAT (h)	26 ± 10	—	—
ARDN	—	—	1.69 ± 0.62

* Median and range
 Immunoassay and noncompartmental methods used

Figure 4 Comparison of Mean ($\pm$ sd) r-hCG Serum Concentration vs. Time Profiles after Single and Multiple Subcutaneous Dosing and when Administered by Different Routes Assessed by Immunoassay



D. Gender Effects

There were no clinically significant gender effects identified after subcutaneous or intravenous administration. However, bioavailability is higher in men after intramuscular administration.

1. Gender Effects after Intravenous Administration

The pharmacokinetics of the phase I liquid formulation of r-hCG was compared to Profasi® (u-hCG) after intravenous administration of a 5000 IU dose in 6 men and 6 women in study 7012. No period or gender effects were detected. However, the number of subjects was small. (See VI.A)

2. Gender Effects after Intramuscular Administration

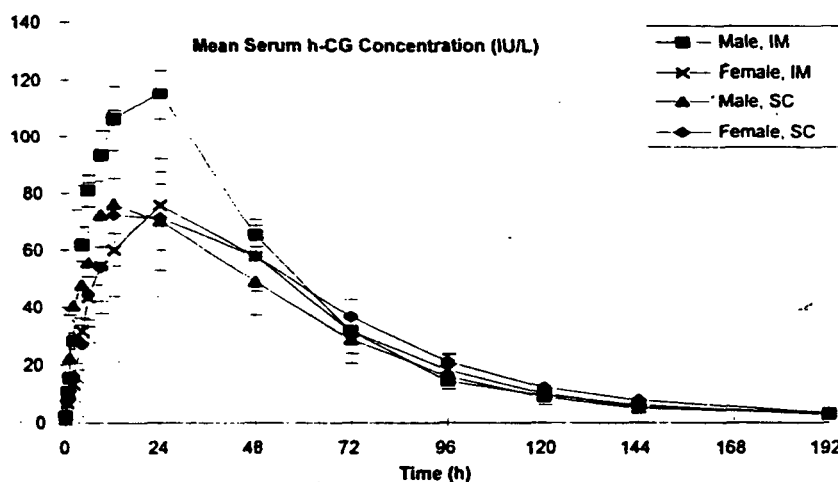
It was observed in study 7013 that absolute bioavailability is higher after IM administration compared to subcutaneous administration and that this higher bioavailability after IM administration is due to greater bioavailability in males. Greater bioavailability in men after IM injection was observed regardless of whether hCG was measured by immunoassay or bioassay (See Error! Reference source not found. and Figure 5). The sponsor speculates that the basis of this gender effect may be that greater adipose tissue in women prevents intramuscular disposition and that drug is actually deposited subcutaneously after 'IM' injection.

Table 14 Effect of Gender and Assay Method on Absolute Bioavailability

Parameter	Immunoassay		Bioassay	
	Route of Administration		Route of Administration	
	IM	SC	IM	SC
F (males & females)	0.47 ± 0.12	0.38 ± 0.10	0.68 ± 0.21	0.56 ± 0.16
F (males)	0.52 ± 0.08	0.37 ± 0.11	0.82 ± 0.10	0.57 ± 0.14
F (females)	0.42 ± 0.14	0.40 ± 0.10	0.55 ± 0.20	0.55 ± 0.20

values are mean ± sd

Figure 5 Mean (±sd) Serum hCG Concentration vs. Time Profiles Following Single Dose (2500 IU) IM and SC Administration to Healthy Male and Female Volunteers (Immunoassay)



The sponsor suggests that the lower bioavailability in women after IM administration and the similarity to the bioavailability after SC administration, is because 'IM' administration in women actually results in the deposition of drug into the subcutaneous fat. This is a plausible hypothesis as based upon the Lorenz formula subjects in this study could be considered obese.

It appears that partly to avoid this gender effect on bioavailability and for patient acceptability, the sponsor has only pursued approval of subcutaneous administration.

3. Gender Effects After Subcutaneous Administration

a) Study 7013

As described in section VI.D.2, in contrast to intramuscular injection there was no effect of gender on the pharmacokinetics of r-hCG after subcutaneous injection.

b) Study 7014

Study 7014 was a phase I single blind, randomized, three-way crossover study, stratified by gender, in 24 healthy volunteers (12 males and 12 females). The primary objective of this study was to assess the bioequivalence of a liquid phase I formulation of r-hCG and a freeze-dried formulation of r-hCG (Ovidrel®) following a single 250 µg SC administration. A second objective was to compare the pharmacokinetics of r-hCG to those of u-hCG (Profasi®) after a comparable single SC injection of 5000 IU (See section VI.H.2).

Each subject received the three single dose treatments in a randomized manner separated by a washout period of three weeks.

The sponsor's analysis of variance did not show any statistically significant differences between the three treatments. However, there was a significant treatment by gender effect ($p < 0.05$) for both Cmax and AUC. In addition, there was a difference in dose administered between the various treatment arms, violating a basic assumption of bioequivalence testing. To adjust for this, the data was reanalyzed using dose-normalized data and by gender. The gender effect detected appears to be due to a gender effect after SC administration of the liquid formulation. There was no gender effect seen with the freeze-dried formulation (see Table 15; and Table 16 and Table 17 for descriptive statistics of the data). In addition, there was a strong sequence effect, but no period effect. Consequently, the washout period may have been insufficient. Additional interpretation of the sequence effect is not possible due to the small numbers of subjects of per sequence ($n = 6/\text{sequence} \ \& \ 3/\text{gender}/\text{sequence}$).

Table 15 Biocomparison of r-hCG to u-hCG after SC Administration (Study 7014)

		Mean Ratio liquid r-hCG to freeze-dried r-hCG		Mean Ratio freeze-dried r-hCG to Profasi® (u-hCG)		Mean Ratio liquid r-hCG to Profasi® (u-hCG)	
		Mean	90% CI	Mean	90% CI	Mean	90% CI
All Subjects	Cmax	1.01	0.92 - 1.10	0.94	0.86 - 1.03	0.95	0.87 - 1.04
	AUC	0.99	0.94 - 1.05	0.99	0.99 - 1.05	0.99	0.93 - 1.05
	DN Cmax	0.94	0.86 - 1.02	0.61	0.56 - 0.66	0.57	0.52 - 0.62
	Clapp	1.08	1.02 - 1.14	1.56	1.47 - 1.65	1.68	1.59 - 1.79
Men	DN Cmax	1.06	0.92 - 1.22	0.62	0.54 - 0.71	0.65	0.57 - 0.75
	Clapp	1.0	0.92 - 1.09	1.53	1.40 - 1.66	1.52	1.40 - 1.66
Women	DN Cmax	0.83	0.74 - 0.92	0.60	0.54 - 0.67	0.50	0.47 - 0.55
	Clapp	1.17	1.08 - 1.27	1.59	1.47 - 1.73	1.86	1.71 - 2.02

Shaded area is sponsor's analysis

DN Cmax - Dose Normalized Cmax

Clapp - Apparent Clearance (Dose/AUC) where F is unknown

Table 16 Pharmacokinetic Metrics of Various Formulations of hCG after SC Administration

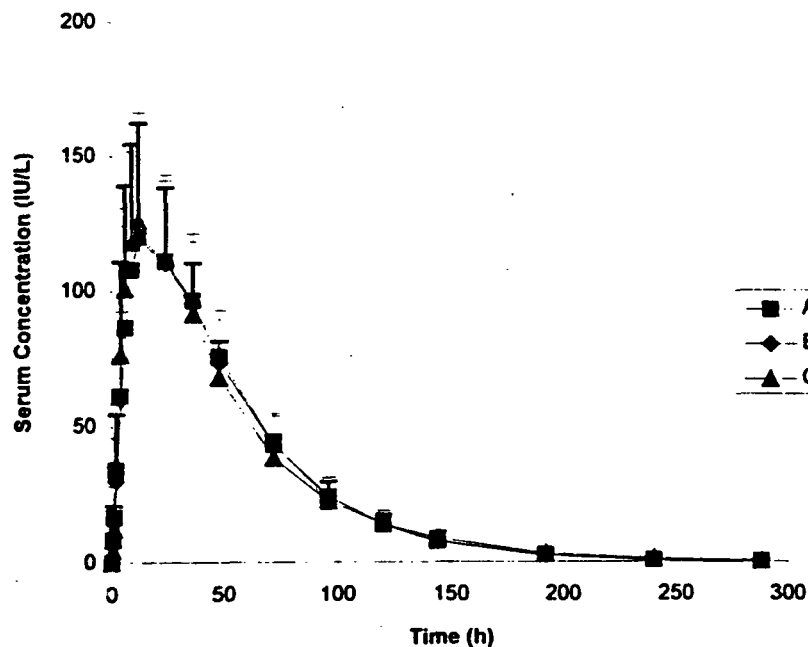
Metric			Treatment		
			Liquid r-hCG	Freeze-dried r-hCG	Profasi® (u-hCG)
Dose	Male	Mean	5172.0	4747.2	3100.2
		SD	179.1	75.9	212.7
		CV(%)	3.5	1.6	6.9
	Female	Mean	5091.7	4804.6	3067.5
		SD	199.3	129.6	132.2
		CV(%)	3.9	2.7	4.3
	All Subjects	Mean	5131.8	4775.9	3083.8
		SD	189.8	107.9	174.0
		CV(%)	3.7	2.3	5.6
Cmax	Male	Mean	145.8	127.9	135.0
		SD	36.9	40.6	41.2
		CV(%)	25.3	31.8	30.5
	Female	Mean	105.8	120.7	123.9
		SD	38.1	44.4	29.6
		CV(%)	36.0	36.8	23.9
	All Subjects	Mean	125.8	124.3	129.5
		SD	42.0	41.8	35.5
		CV(%)	33.4	33.6	27.4
DN Cmax	Male	Mean	0.0283	0.0270	0.0434
		SD	0.0076	0.0087	0.0122
		CV(%)	27.0	32.2	28.2
	Female	Mean	0.0208	0.0251	0.0404
		SD	0.0074	0.0091	0.0093
		CV(%)	35.5	36.2	22.9
	All Subjects	Mean	0.0245	0.0260	0.0419
		SD	0.0083	0.0087	0.0107
		CV(%)	33.8	33.6	25.6
AUC	Male	Mean	8782.9	7996.3	8035.7
		SD	1686.7	1141.3	1650.1
		CV(%)	19.2	14.3	20.5
	Female	Mean	6989.8	7700.7	7684.7
		SD	1894.3	2100.8	1513.6
		CV(%)	27.1	27.3	19.7
	All Subjects	Mean	7886.3	7848.5	7860.2
		SD	1978.8	1660.3	1558.9
		CV(%)	25.1	21.2	19.8
Clapp (Dose/AUC)	Male	Mean	0.611	0.606	0.401
		SD	0.132	0.094	0.93
		CV(%)	21.5	15.5	23.2
	Female	Mean	0.784	0.674	0.414
		SD	0.233	0.165	0.087
		CV(%)	29.7	25.7	21.1
	All Subjects	Mean	0.698	0.640	0.408
		SD	0.205	0.165	0.089
		CV(%)	29.4	25.7	21.7

Table 17 Additional Pharmacokinetic Metrics of Various Formulations of hCG after SC Administration

Parameter (mean $\pm$ sd)	Liquid r-hCG	Freeze dried r-hCG	Profasi® (u-hCG)
t_{max} * (males) (h)	12 (9-36)	12 (9-24)	12 (6-36)
t_{max} * (females) (h)	24 (12-24)	24 (12-24)	12 (9-24)
t_{max} * (h)	12 (9-36)	12 (9-24)	12 (6-36)
λ_z (males) (h^{-1})	0.023 (0.004)	0.023 (0.004)	0.019 (0.002)
λ_z (females) (h^{-1})	0.026 (0.005)	0.025 (0.005)	0.021 (0.004)
λ_z (h^{-1})	0.024 (0.005)	0.024 (0.005)	0.020 (0.004)
$t_{1/2}$ (males) (h)	31 (5)	31 (5)	37 (4)
$t_{1/2}$ (females) (h)	28 (5)	29 (6)	34 (6)
$t_{1/2}$ (h)	29 (5)	30 (5)	35 (6)
MRT (males) (h)	51 (7)	53 (8)	53 (5)
MRT (females) (h)	53 (10)	53 (10)	53 (7)
MRT (h)	52 (8)	53 (9)	53 (6)

Although gender effects were detected in this study they should not be clinically significant. In addition, in spite of the difference in the actual doses administered, based upon the nominal dose that was administered the exposures were comparable between the various treatments (See Figure 6).

Figure 6 Comparison of Mean ($\pm$ SD) Serum hCG Concentration vs. Time Profiles Following Single Dose Administration of Two Formulations of r-hCG and u-hCG



A=5000 IU SC of r-hCG as a liquid formulation
B=5000 IU SC of r-hCG as a freeze dried formulation
C=5000 IU SC of u-hCG (Profasi®)

c) Study 21443

Study 21443 examined the bioequivalence of a 250 µg and a 500 µg formulation when administered as a 500 µg subcutaneous injection below the umbilicus. Neither period-by-gender nor treatment-by-gender interactions were detected in this study.

E. Comparison of Pharmacokinetics When Assessed by Immunoassay and Bioassay Method

Both the immunoassay and the bioassay for hCG depend upon hCGs structure. Since r-hCG is composed of both major and minor species, it should not be surprising if both analytical and pharmacokinetic measurements should vary when assessed by the immunoassay compared with the bioassay. By extension, it would also not be surprising if pharmacokinetics and even pharmacodynamics differ between u-hCG and r-hCG.

When compared, concentration vs. time profiles for r-hCG appear similar whether based upon immunoassay data or bioassay data, although upon close inspection there are obvious differences in the graphs (See Figure 7 and Figure 8).

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Figure 7 Mean plot of serum hCG concentration-time data ($\pm$ SD) following single dose (A= 2500 IU IV, B= 2500 IU IM and C= 2500 IV SC) and multiple dose (D= 2500 IU every 48 hours SC) administration of r-hCG (Immunoassay)

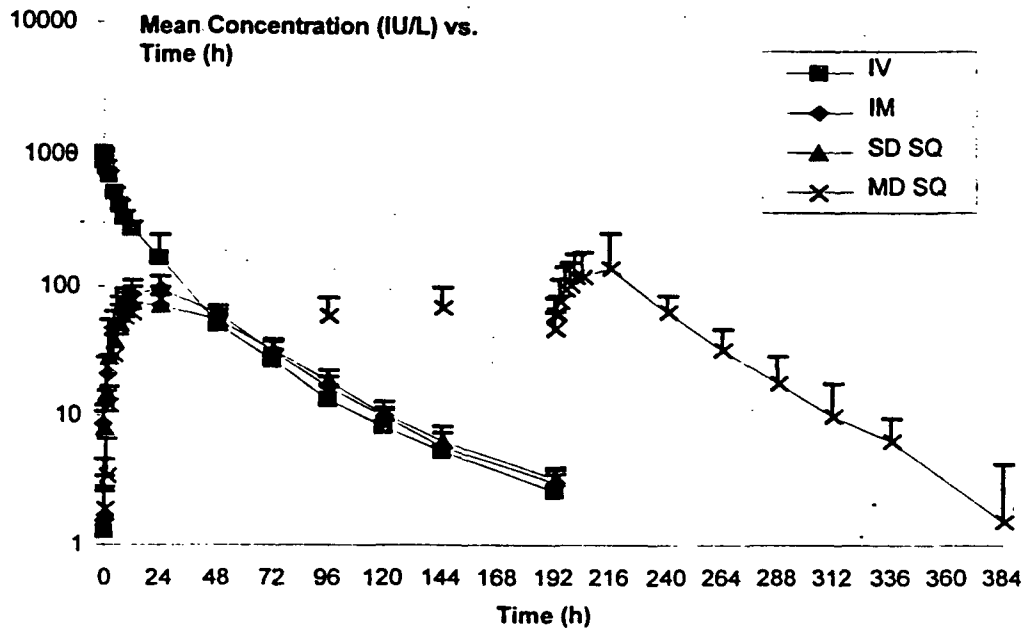
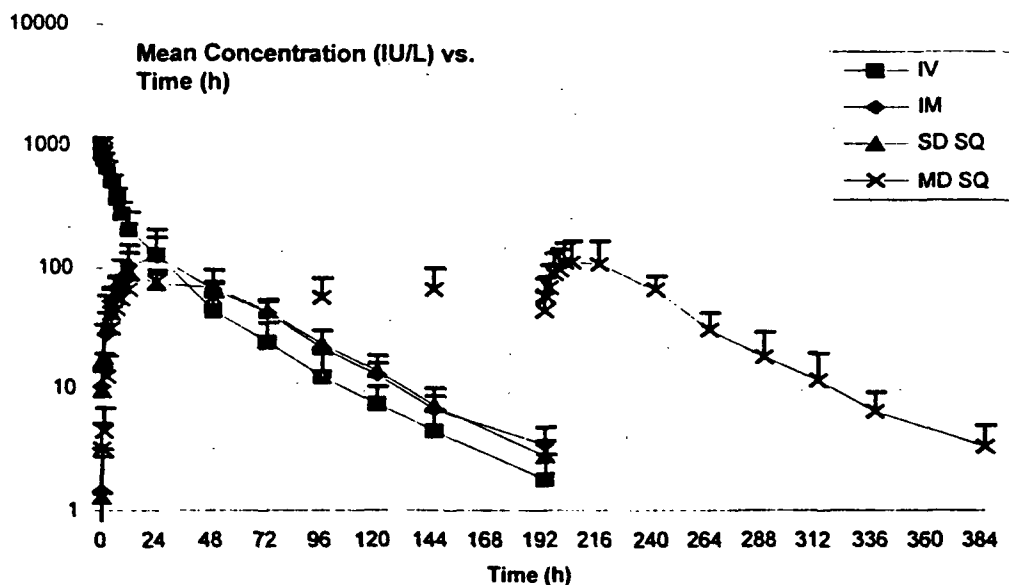


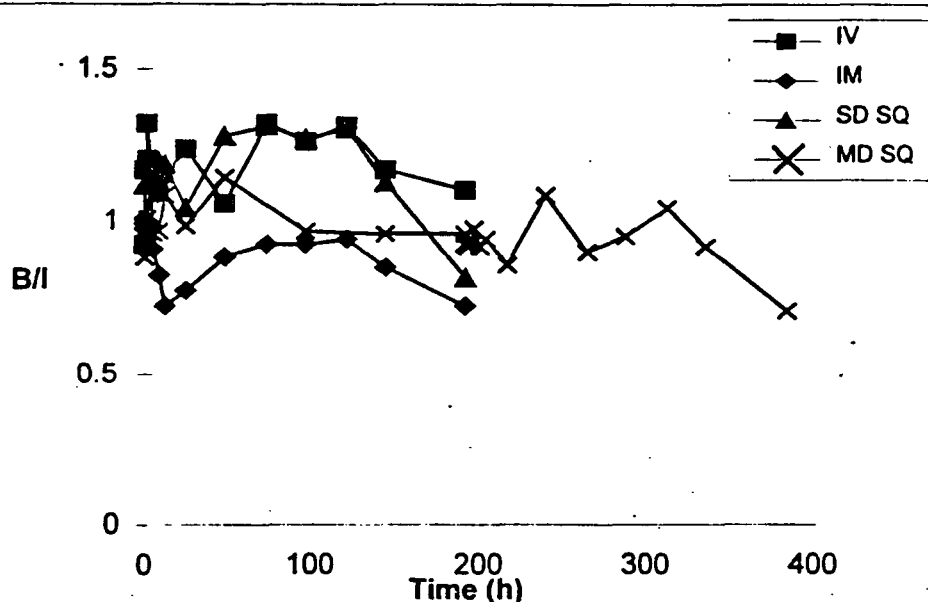
Figure 8 Mean plot of serum hCG concentration-time data ($\pm$ SD) following single dose (A= 2500 IU IV, B= 2500 IU IM and C= 2500 IV SC) and multiple dose (D= 2500 IU every 48 hours SC) administration of r-hCG (bioassay)



When mean bioassay to immunoassay concentration ratios (B/I ratio) are plotted vs. time for each route of administration, it's apparent that there is systematic assay bias in different directions with different routes of administration (See Figure 9). For example The B/I ratio is 1 or less for IM administration and greater than 1 for IV administration.

In addition, regardless of the route of administration the B/I ratio shows similar general patterns over time. There is an initial decline in B/I ratio, followed by a trough, an increase in the ratio, a plateau phase, and a final decline in the ratio that is largely independent of route of administration (See Figure 9).

Figure 9 Mean B/I Ratio vs. Time for r-hCG for Different Routes of Administration



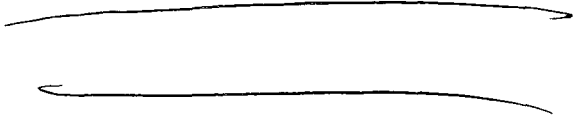
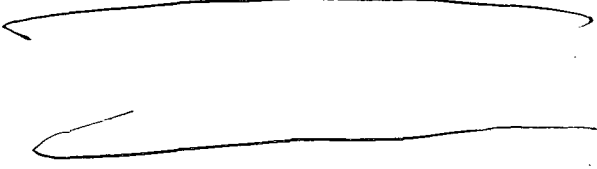
Although these patterns are generally similar, they are not exactly the same. These patterns may reflect differences in the pharmacokinetics of different major and minor species; and differences in the pharmacokinetics of the different species with different routes of administration.

It's also likely that there are even more differences when the source of hCG, i.e. u-hCG or r-hCG are similarly compared.

As expected, when total hCG is measured there are differences in calculated pharmacokinetic metrics when different assay methods are used. However, these differences in pharmacokinetic metrics are only significant differences in two cases.

In one case, the difference is in the steady-state AUC after multiple dose subcutaneous administration. In this situation when the bioassay is used, the steady-state AUC is much lower than the single dose AUC, thus indicating possible induction or decreased bioavailability over time (See Table 18).

Table 18 Comparison of Pharmacokinetic Metrics as Assessed by Immunoassay and Bioassay after Multiple Dose Subcutaneous Administration

Parameter	Immunoassay	Bioassay
		
First Dose AUC _{0-∞} (IU·h·L ⁻¹)	5123 ± 958	6322 ± 1442
AUC _{0-∞} DN (h·L ⁻¹)	1.92 ± 0.39	2.47 ± 0.64
		

* Median and range

In the other case, the difference in pharmacokinetic metrics observed between the immunoassay and the bioassay is a greater degree of bioavailability with the bioassay upon single dose administration (See Table 14).

It's notable that in virtually every subject the dose administered is lower when assessed by bioassay than when assessed by immunoassay. This in combination with the higher measured bioavailability, indicate complex differences in pharmacokinetics between different routes of administration and probably with drug source. One possible explanation is differences in formation of an active metabolite that is not detected by the immunoassay, although this hypothesis cannot be confirmed with the current data and assay methods.

F. Renal

Renal elimination was examined in studies 7012 and 8927. Renal clearance is approximately 30 ml / minute and accounts for approximately 12% of the administered dose. It is also independent of dose over the range of 500 to 44,000 IU. Renal pharmacokinetic metrics from these studies are shown in Table 19.

Table 19 Renal Pharmacokinetic Metrics of hCG After Intravenous Administration

Drug Substance	r-hCG				u-hCG
Study	7012			8927	7012
Nominal Dose	500 IU 25 µg	5000 IU 250 µg	20,000 IU 1000 µg	44,000 IU "2000 µg"	5000 IU —
Administration	IV			IV over 3 minutes	IV
Metric Units	Healthy Volunteers 6/6 M/F			4 Healthy Females 17 - 45 yo	Healthy Volunteers 6/6 M/F
$t_{1/2}(1)$ (h)	3.9 ± 0.7	4.7 ± 0.8	5.0 ± 0.7	4.5 ± 0.7	5.0 ± 0.7
$t_{1/2}$ (h)	23 ± 4	28 ± 3	30 ± 2	29.0 ± 4.6	33 ± 3
CL (L·h ⁻¹)	0.28 ± 0.05	0.31 ± 0.04	0.33 ± 0.04	0.226 ± 0.18	0.33 ± 0.05
MRT (h)	20 ± 3	22 ± 3	23 ± 2	28.6 ± 3.6	23 ± 2
V _c (L)	2.9 ± 0.6	3.4 ± 0.7	3.8 ± 0.7	3.4 ± 0.7	3.8 ± 0.7
V _{ss} (L)	5.7 ± 1.1	6.7 ± 1.2	7.7 ± 1.4	6.5 ± 1.15	7.7 ± 1.4
Cl _r ml/hr	34 ± 10	28 ± 12	29 ± 8	28.8 ± 6.2	30 ± 8
f _e (%)	11.9 ± 2.6	9.1 ± 3.4	11.5 ± 3.9	12.9 (10.1 - 17.3)	9.0 ± 2.5

The similar pharmacokinetic metrics across doses and studies is also strongly suggestive of dose linearity.

G. Nonrenal Elimination

The sponsor reports that a number of possible urinary metabolites of u-hCG have previously been reported in the literature. These include:

free α subunits
free β subunits



hCGβcf consists of two polypeptide chains, β chain amino acids — 92 and β chain amino acids — noncovalently linked by disulfide bonds.

According to the sponsor ————— times as potent as hCG.

In study 8927 1.7% of the administered dose of 44,000 IU r-hCG was eliminated as hCGβcf (range 0.8 - 2.9%) in the urine. In addition, hCGβcf was found circulating in plasma. This suggests an average formation clearance of approximately 3.9 ml / hr assuming total urinary elimination and linear kinetics, the

latter is a notable assumption since the dose in this study is so much higher than the proposed therapeutic dose.

H. Comparison of r-hCG and u-hCG Pharmacokinetics

It's unclear how the pharmacokinetics of r-hCG compares with u-hCG, and the implications.

A classical pharmacokinetic study examining intravenous administration (study 7012) demonstrated increased clearance with r-hCG.

Study 7014, which compared subcutaneously administered r-hCG with u-hCG, also found lower Cmax's and higher apparent clearances for r-hCG compared to u-hCG for both men and women.

In a population study GF 7648, 'Comparison of Pharmacokinetics of r-hCG with u-hCG after SC Administration Population Analysis in Women Undergoing Infertility Treatment', a larger AUC was observed with r-hCG compared with u-hCG. This difference in AUC is in the opposite direction from that observed in a classical pharmacokinetic study with intravenous administration (study 7012) and with subcutaneous administration (study 7014).

This higher AUC with r-hCG in study GF 7648 is due to a combination of lower V/F (79.3%) and Cl/F (82.3). Consequently, it could be due to differences in F. Alternatively, since the actual dose administered was not verified, the difference could be due to differences in dose and thus spurious.

In addition, the sponsor claims that the findings in the reported population PK study (GF 7648) is opposite to that observed in the US based phase III study (GF 7927), however no data was presented for the US study.

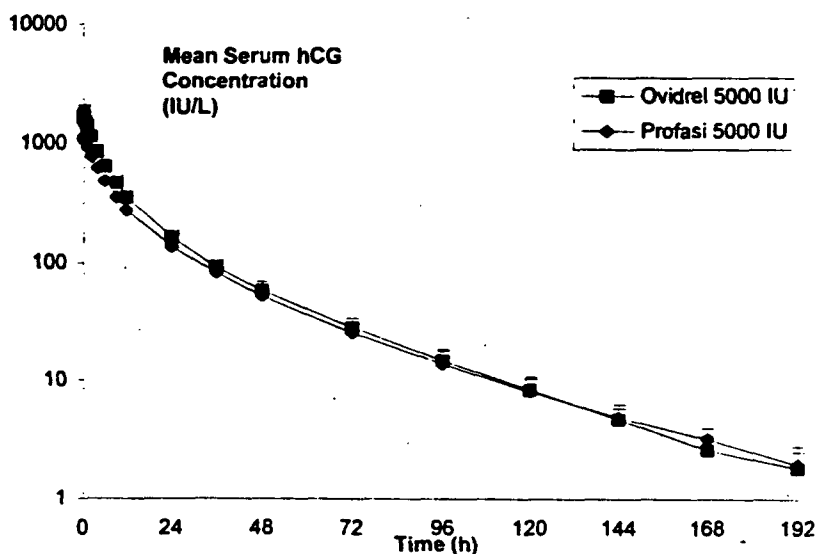
In conclusion, it's unclear how the pharmacokinetics of r-hCG compares with u-hCG, although there may very well be some pharmacokinetic differences. Even if there are differences in exposure the clinical implications are not clear, due to the possibility of slightly different activities.

1. Comparison of r-hCG and u-hCG after Intravenous Administration

The pharmacokinetics of the phase I liquid formulation of r-hCG was compared to Profasi® (u-hCG) after intravenous administration of a 5000 IU dose in 6 men and 6 women in study 7012.

Both r-hCG and Profasi® (u-hCG) demonstrated similar biphasic pharmacokinetic profiles (See Figure 10).

Figure 10 Mean ($\pm$ sd) Concentration-Time Data Following IV Administration of 5000 IU Ovidrel® or Profasi®



Analysis of variance of log transformed dose normalized AUC as calculated by a noncompartmental approach showed a significant difference between r-hCG and u-hCG after intravenous administration ($p = 0.013$ - Study 7012), indicating a difference in pharmacokinetics. Specifically, the total body clearance of Ovidrel® (r-hCG) is on average more than 10% greater. This results in a shorter terminal half-life for Ovidrel® (r-hCG). This difference in kinetics is likely due to a difference in the minor species and/or tertiary structure of recombinant and biologically sourced hCG. There were no period or gender effects in spite of the fact that all women were receiving oral contraceptives.

Pharmacokinetic metrics are summarized in Table 20. The difference in the pharmacokinetic metrics is highlighted by the Profasi® to r-hCG AUC ratio (u-hCG/r-hCG) of 0.79, which is greater than the dose ratio of 0.63; this gives a dose normalized ratio of 1.27.

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Table 20 Comparison of Compartmental Pharmacokinetic Metrics of Ovidrel® (r-hCG) and Profasi® (u-hCG) after IV administration (Study 7012)

Drug Nominal Dose		Ovidrel® 5000 IU	Profasi® 5000 IU	Profasi to Ovidrel Ratio
Dose	IU ^a	5130 ± 166	3231 ± 167	0.63
	µg	270 ± 9	170 ± 9	
C ₁	(IU·L ⁻¹)	1399 ± 317	906 ± 209	
	(µg·L ⁻¹)	75.4 ± 16.3	48.4 ± 11.2	
λ ₁	(h ⁻¹)	0.151 ± 0.023	0.1345 ± 0.048	
t _{1/2} (1)	(h)	4.7 ± 0.8	5.5 ± 1.3	
C ₂	(IU·L ⁻¹)	192 ± 60	139 ± 45	
	(µg·L ⁻¹)	10.5 ± 2.9	7.5 ± 2.4	
λ ₂	(h ⁻¹)	0.025 ± 0.003	0.023 ± 0.002	
t _{1/2}	(h)	28 ± 3	31 ± 3	
AUC	(IU·h·L ⁻¹)	16804 ± 2356	13255 ± 3147	0.79
	(µg·h·L ⁻¹)	899 ± 118	706 ± 170	0.79
DN AUC	(L·h ⁻¹)	3.28 ± 0.45	4.09 ^a	1.27
CL	(L·h ⁻¹)	0.31 ± 0.04	0.27 ± 0.13	
CL _r	(L·h ⁻¹)	0.028 ± 0.012	0.029 ± 0.008	
fe	(%)	9.1 ± 3.4	11.5 ± 3.9	
MRT	(h)	22 ± 3	25 ± 2	
V _c	(L)	3.4 ± 0.7	3.2 ± 0.7	
V _{ss}	(L)	6.7 ± 1.2	6.6 ± 2.6	

- a Dose measured by immunoassay
 * estimated from mean dose and mean AUC

2. Comparison of Pharmacokinetics of r-hCG with u-hCG after SC Administration to Healthy Male and Female Volunteers

Study 7014 was a phase I single blind, randomized, three-way crossover study, stratified by gender, in 24 healthy volunteers (12 males and 12 females). The primary objective of this study was to assess the bioequivalence of a liquid phase I formulation of r-hCG and a freeze-dried formulation of r-hCG (Ovidrel®) following a single 250 µg SC administration. A second objective was to compare the pharmacokinetics of r-hCG to those of u-hCG (Profasi®) after a comparable single SC injection of 5000 IU (See section VI.D.3.b)).

Each subject received the three single dose treatments in a randomized manner separated by a washout period of three weeks.

The sponsor's analysis of variance did not show any statistically significant differences between the three treatments. However, there was a difference in dose administered between the various treatment arms, thus violating a basic assumption of bioequivalence testing. In addition, there was a significant treatment by gender effect ($p < 0.05$) for both C_{max} and AUC. To adjust for this the data was reanalyzed using dose-normalized data (See Table 15, Table 16, and Table 17)

When dose normalized data is compared, the dose normalized C_{max}'s of r-hCG are approximately 50-66% of the dose normalized C_{max}'s achieved with u-hCG, and ratio is similar for both men and women. Similarly, the ratios of apparent clearance are in the opposite direction, with apparent clearances of approximately 1.4 to 2.0 fold higher with r-hCG.

As mentioned previously, there was a strong sequence effect, but no period effect. Consequently, the washout period may have been insufficient. Additional interpretation of the sequence effect is not possible due to the small numbers of subjects of per sequence ($n = 6/\text{sequence} \ \& \ 3/\text{gender}/\text{sequence}$).

See section VI.D.3.b) for a discussion of the gender effect.).

In spite of the difference in the actual doses administered, based upon the nominal dose that was administered the exposures were comparable between the various treatments (See Figure 6).

3. Comparison of Pharmacokinetics of r-hCG with u-hCG after SC administration Population Analysis in Women Undergoing Infertility Treatment

Population pharmacokinetic analysis in study GF 7648 showed a greater exposure to hCG after SC administration of r-hCG compared with u-hCG. Specifically, the sponsor claims that AUC 21.6% higher after r-hCG compared with u-hCG, and that this is due to a combination of lower apparent clearance after SC administration of r-hCG and 20.7% lower V/F (See Table 21 and Table 22). The basis for this finding is unclear, although the results need to be interpreted cautiously, especially due to the sparse early sampling, poor estimates of the absorption phase and early exposure, and lack of documentation of the actual dose administered.

A comparison of the pharmacokinetics of the to-be-marketed freeze-dried r-hCG formulation with u-hCG (Profasi®) after SC administration in women undergoing infertility treatment was performed as a population PK substudy of the phase III clinical efficacy trial in Europe (Study GF 7648).

97 women received r-hCG and 93 subjects u-hCG prior to In Vitro Fertilization and Embryo Transfer. Nominal doses of 250 µg r-hCG or 5000 IU u-hCG was administered at night (around 9PM) subcutaneously just below the umbilicus. Blood samples for determination of serum hCG concentrations were obtained at around 8 AM the following morning then daily thereafter for a total of 4 doses.

An underlying structural model of an open one-compartment model with first order absorption was found to best fit the data. Covariates that were examined included treatment, smoking status, age, height, weight, body mass index (BMI), and body surface area (BSA). There was insufficient subject heterogeneity to assess the effects of race. The only two covariates retained in the final model were treatment and the effect of BMI on volume of distribution for u-hCG but not for r-hCG. Due to the inadequate sampling during the absorption phase estimates of inter-individual variability was not possible.

Table 21 Population Estimates of Pharmacokinetic Metrics

Metric	Units	r-hCG		u-hCG	
		Pop Mean	95% CI	Pop Mean	95% CI
Ka	hr-1	0.102	0.088, 0.115	0.086	0.067, 0.104
K	hr-1	0.025	0.024, 0.026	0.0234	0.022, 0.024

Table 22 Post-hoc Analysis of Population Pharmacokinetic Metrics

Metric	Units	Summary Statistic	r-hCG	u-hCG	Difference	95% CI
t1/2 _{absorption}	hr	not specified	8	7	—	—
t1/2	hr	Median	29.2	27.8	—	—
AUC	µg/ml • hr-1	Mean	513	422	91	39, 146
C1/F	L/hr	Median	0.51	0.66	—	—
V1/F	L	Median	21.4	27.0	—	—

The higher AUC with r-hCG is due to a combination of lower V1/F (79.3%) and C1/F (82.3). Consequently, it could be due to differences in F. Alternatively, since the actual dose administered was not verified and the dosing instructions were unclear, the difference could be due to differences in dose. Dosing instructions for study GF 7648 call for the dilution of 285 mcg of r-hCG with 1 ml of SWI. However, the volume to be administered is not defined. Consequently, if the contents of the vial are administered, the nominal dose is 285 mcg and not 250 mcg as claimed.

In addition, the sponsor claims that the findings in the reported population PK study (GF 7648) are opposite to those observed in the US based phase III study (GF 7927), however no data was presented for the US study.

VII. PHARMACODYNAMICS

The pharmacodynamics of r-hCG are complex as there are numerous pharmacologic effects. Pharmacodynamic effects vary by route of administration and by gender, and appear to be time variant. Results of pharmacodynamic studies are described in detail in APPENDIX 3 - PHARMACODYNAMICS. Pharmacodynamic studies in men indicate that the dosage range chosen for r-hCG for the present indication in women should be similar to the range for u-hCG. In addition, maximal effects for at least some pharmacologic effects may be obtained at less than the maximal doses of 10,000 IU currently employed clinically.

A. Liquid and Freeze-Dried Formulations

developed although not completely explaining the relationships, none-the-less do provide useful information.

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X. LABELING COMMENTS

Text with a single ~~strike through~~ is to be deleted.

Underlined text is to be added.

Sponsor's Initial Proposal	OCPB Reviewer's Response	Comments
Pharmacokinetics When given by intravenous administration, the pharmacokinetic profile of Ovidrel® ~~follows~~ a biexponential model.	Pharmacokinetics When given by intravenous administration, the pharmacokinetic profile of Ovidrel® ~~follows~~ a biexponential model.	• Rearranged for clarity • Values did not match study reports

Sponsor's Initial Proposal	OCPB Reviewer's Response	Comments
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Table 23: Pharmacokinetic Parameters (mean $\pm$ SD) of hCG after Single-Dose Administration of Ovidrel® in Healthy Female Volunteers

Route of Administration	

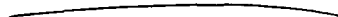
C_{max} : peak concentration (above baseline), t_{max} : time of C_{max} , AUC: total area under the curve, $t_{1/2}$: elimination half-life, F: bioavailability

* median (range)

Sponsor's Initial Proposal	OCPB Reviewer's Response	Comments
Absorption Following subcutaneous administration of Ovidrel®, maximum serum concentration is reached after approximately 12 hours. The mean absolute bioavailability of Ovidrel® following a single subcutaneous injection to healthy female volunteers is about 40%.	Acceptable	
Distribution [Handwritten marks: 7, L, J]	Distribution [Handwritten marks: 7, L]	Self explanatory
Metabolism/Excretion [Handwritten marks: 7, L, J]	Metabolism/Excretion [Handwritten marks: 7, L]	- Accumulation ratio calculated incorrectly. Sponsor needs to recalculate, using $AUC_{0-\infty}$ for the first dose instead of AUC_{0-48} in the formula utilized. Sponsor should provide raw data with the recalculations. - Time to steady state should include range. - Additional comment self explanatory

Sponsor's Initial Proposal	OCPB Reviewer's Response	Comments
	<u>detected.</u> One-tenth of the Ovidrel® dose is excreted in the urine.	
Pharmacodynamics _____ in female subjects on oral contraception, Ovidrel® induced a clear increase in androstenedione serum levels. _____ _____ Pharmacodynamic studies in both males and females determined that the pharmacologic effect of Ovidrel® _____	Pharmacodynamics _____ In female subjects on oral contraception, <u>after an initial latency period,</u> Ovidrel® induced a clear increase in androstenedione serum levels. _____ <u>24 hours after dosing.</u> _____ Pharmacodynamic studies in both males and females determined that the <u>relationship of Ovidrel® pharmacokinetics to pharmacologic effect of Ovidrel® _____ are complex and vary with the pharmacodynamic marker examined. In general pharmacologic effects are not proportional to exposure and in some cases appear to be near maximal at a 250 mcg dose.</u>	• _____ • Self explanatory
Population pharmacokinetics and pharmacodynamics: In _____ Ovidrel® _____ subcutaneously to trigger ovulation, the results of a population PK/PD analysis _____ _____ generally supported the data obtained in healthy subjects. Pharmacokinetic	Population pharmacokinetics and pharmacodynamics: In _____ Ovidrel® _____ subcutaneously to trigger ovulation, the results of a population PK/PD analysis _____ _____ generally supported the data obtained in healthy subjects. Pharmacokinetic	• Mean and median included for clarification. • Median value for Vdapp with u-hCG corrected. • The values provided are suspect due to the sampling scheme, however these are the values found and issues with parameter estimates are usual pop PK analyses. Differences in values from those reported elsewhere could be due to this and due to

Sponsor's Initial Proposal	OCPB Reviewer's Response	Comments
parameters for Ovidrel® include _____ _____ apparent volume of distribution: _____	parameters for Ovidrel® include _____ _____ ¹ median apparent volume of distribution: _____	reporting of apparent values (i.e. uncorrected for bioavailability). However, these are the only values in the patient population so in spite of the inconsistency with values reported elsewhere in the labeling, this section may be retained.
Special populations: Safety, efficacy, and pharmacokinetics of Ovidrel® in patients with renal or hepatic insufficiency have not been established.	Acceptable	
Drug-Drug Interactions: No drug-drug interaction studies have been conducted. _____ _____ Administration of Ovidrel® may interfere with the interpretation of pregnancy tests.	Drug-Drug Interactions: No drug-drug interaction studies have been conducted. _____ _____ Administration of Ovidrel® may interfere with the interpretation of pregnancy tests. (see PRECAUTIONS).	- As a matter of policy, statements regarding interactions that have not been observed are generally not allowed. Observation of this sort are not rigorous and may result in false reassurances. - see Precautions statement. moved from before to after the appropriate sentence.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if hCG is administered to a nursing woman.	Acceptable	
Pediatric Patients: Safety and effectiveness in	Acceptable	

Sponsor's Initial Proposal	OCPB Reviewer's Response	Comments
pediatric patients has not been established.		
Geriatric Patients: Safety and effectiveness in geriatric patients has not been established.	Acceptable	
DOSAGE AND ADMINISTRATION <i>For Subcutaneous Use Only</i> ...   	DOSAGE AND ADMINISTRATION <i>For Subcutaneous Use Only</i> ...   	Administration instructions should reflect how administered in phase III and pivotal bioequivalence studies

XI. SIGNATURES

/S/

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

9/7/00
Date

/S/

Ameeta Parekh, Ph.D.

Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

9/9/00
Date

OCPB Briefing Meeting: Monday August 7, 2000 3:30 PM PKLN 13B-17

Attendees: Parekh, A; Kavanagh, R; Huang, S; Hunt, J

CC: NDA 21-149 (orig., 1 copy)
HFD-580 (DeGuia, Bennett, Slaughter, Kammerman)
HFD-510 (Yang)
HFD-850 (Lesko)
HFD-870 (Huang, Hunt, Kavanagh, Parekh)
Central Document Room (Barbara Murphy)

APPENDIX 1 - OVERVIEW OF HUMAN CHORIONIC GONADOTROPIN

XII. APPENDIX I - OVERVIEW OF HUMAN CHORIONIC GONADOTROPIN

A. Human Chorionic gonadotropin - Overview

Human Chorionic gonadotropin (hCG) is a reproductive hormone produced by trophoblasts as early as 6 days post-conception. In early pregnancy hCG prolongs the life of the corpus luteum and activates the secretion of estrogen and progesterone by this organ until this function is assumed by the placenta itself.

B. Physiologic Actions

Human Luteinising Hormone and hCG initiate their activity by first binding to a specific glycoprotein component of the cell plasma membrane called the LH/hCG receptor. The kinetics of binding of hCG to the LH/hCG receptor depend on specific structural features of hCG. Proper LH/hCG receptor interaction is necessary for initiation of intracellular mechanisms that regulate biochemical processes in the ovary (theca and granulosa cells) and the testis (Leydig cell).

In these cells, binding of human Luteinising Hormone and hCG to the LH/hCG receptor, stimulates the adenylylase enzymatic system located on the internal membrane to transform adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP). cAMP then stimulates the transformation of an inactive protein kinase which itself stimulates the beginning of steroidogenesis in the mitochondria by transforming cholesterol into pregnenolone. In the corpus luteum this results in the formation of estrogen and progesterone, and in the Leydig cells of the testes this results in the production of testosterone.

C. Pharmacologic Uses

Due to its biological similarity to human Luteinising Hormone, hCG has been clinically used in both men and women.

In hypogonadotropic men, hCG (and human Menopausal Gonadotropin) has been used as exogenous gonadotropin therapy for stimulation of testicular functions. By binding to the LH/hCG receptor of the Leydig cells it stimulates the production of testosterone, which secondarily induces spermatogenesis.

In women, urinary human Chorionic Gonadotrophin (u-hCG) induces final follicular maturation and triggers ovulation in patients receiving infertility therapy. It has also been administered after ovulation to provide hormonal support for the corpus luteum.

APPENDIX 2 - CHEMISTRY

5 page(s) have been
removed because it
contains trade secret
and/or confidential
information that is not
disclosable.

(b4)

APPENDIX 3 - PHARMACODYNAMICS

17 page(s) have been
removed because it
contains trade secret
and/or confidential
information that is not
disclosable.

(b4)

NDA 21-149

Ovidrel® (choriogonadotropin alfa for injection)

Serono Laboratories

Abuse Liability Review

Ovidrel® does not have the potential for abuse. No studies related to overdosage have been conducted and no episodes of overdosage have been reported.