CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-367

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

MEMORANDUM

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

Date: October 18, 2002

From: Ameeta Parekh, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Subject: Cover Memorandum for NDA 21-367, Estradiol Acetate Vaginal Ring for HRT

To: NDA: 21-367

The OCPB briefing for NDA 21-367 was held on 10/7/02. Dr. Sayed AlHabet was the primary reviewer for the Clinical Pharmacology and Biopharmaceutics review of this NDA. Several comments were raised at the briefing, some of which have been addressed in the attached review by Dr. Al Habet. Since Sayed had a family emergency, he was unable to incorporate all the changes recommended. I have discussed the labeling comments with Dr. Theresa Van der Vlugt (primary Medical Officer) and conveyed our comments that have been incorporated in the label.

Specifically, the in-vitro release methodology and specifications (also addressed in the chemistry review) were to be added to the review as follows:

Dissolution Method – In-Vitro Release Rate Determination

Dissolution Procedure: Method ——— Volume 1.5 of the NDA; page 928]

Dissolution Analytical Method, Method ——— [1.5:920]
Method for Determination of Estradiol-3-Acetate as 17-beta-Estradiol anhydrous, mcg/day, by ——

The estradiol-3-acetate is hydrolyzed to estradiol just before analysis by — The amount present in the solution is determined by — The average release rate is calculated for each ring, and the mean rate of the — rings is reported as the in vitro release rate.

[ ]

[ ]

Sampling: The number of rings for each test: —

Acceptance Criteria: As described in the table below.

Acceptance Criteria – 0.050 mg/day and 0.10 mg/day

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WITHHOLD 1 PAGE (S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-367	Brand Name	[redacted]
OCPB Division I	HFD-870	Generic Name	Estradiol acetate
Medical Division	HFD-580	Drug Class	Hormone
OCPB Reviewer	Sayed Al-Habet, Ph.D.	Indication(s)	Vasomotor Symptoms
OCPB Team Leader	Ameeta Parekh, Ph.D.	Dosage Form	Vaginal Ring (0.5 mg/day)
		Dosing Regimen	Once ever 3 month
Date of Submission	December 21, 2001	Route of Administration	Vagina
Estimated Due Date of OCPB Review	September 1, 2002	Sponsor	Galen
PDUFA Due Date	December 21, 2002	Priority Classification	3S
Division Due Date	September 30, 2002		

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.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	1		
Patients-				
single dose:	X	1		
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
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		8		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1) What is the effect of rings shelf life (age) on estradiol release rate? 2) What is the clinical significance of early estradiol surge and its effects on hemostatic and coagulation parameters? 3) How much of estradiol acetate (the parent drug) is detected in the blood?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Sayed Al-Habet, Ph.D.**	
Secondary reviewer Signature and Date	**Ameeta Parekh, Ph.D.**	

CC: NDA 21-289, HFD-850 (p. Lee), HFD-580 (Spell-LeSane), HFD-870 (Al-Habet, Parekh, Malinowski, Hunt), CDR (B. Murphy, biopharm file)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
(Draft, July 2002)

NDAs: 21-367
Category: 3S

Submission Date:
December 21, 2001
August 23, 2002
August 30, 2002
September 11, 2002
September 12, 2002
September 23, 2002
October 1, 2002
October 9, 2002 (fax)

Generic Name: Estradiol Acetate

Brand Name: ——— (Estradiol Acetate)

Formulations: Vaginal Ring

Route of Administration: Vaginal

Indication: Vasomotor Symptoms in Post-menopausal Women

Sponsor: Gallen, Inc.
Rockaway, NJ

Type of Submission: New Viginal Formulation (3S)

Reviewer: Sayed Al Habet, Ph.D.

Dates of Review:

Received for Review: February 6, 2002
First Draft: August 19, 2002
Second Draft: September 9, 2002
Briefing Draft:
Final/DFS Version:

Synopsis:

[redacted] (estradiol acetate vaginal ring) or [redacted] (as originally submitted name) is a soft and flexible polymer ring that contains a central core of estradiol acetate. There are two strengths: [redacted] 0.05 mg/day and 0.1 mg/day. The 0.05 and 0.1 mg/day strengths contain 12.4 mg or 24.8 mg of estradiol acetate, which releases at a rate equivalent of 0.05 mg or 0.1 mg of estradiol per day for 3 months, respectively. The sponsor proposed the following indications for these products: 1) moderate to severe vasomotor symptoms and 2) [redacted]

RECOMMENDATION:

Based on the information submitted this NDA was found acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

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Executive Summary
Clinical Pharmacology and Biopharmaceutics

Background:

[redacted] (estradiol acetate vaginal ring) is a soft and flexible polymer ring that contains a central core of estradiol acetate. Estradiol acetate is considered as a pro-drug for releasing estradiol in the systemic circulation.

The sponsor is proposing to market two strengths: [redacted] 0.05 mg/day and [redacted] 0.1 mg/day. The 0.05 and 0.1 mg/day strengths contain 12.4 mg or 24.8 mg of estradiol acetate, which releases at a rate equivalent to 0.05 mg or 0.1 mg of estradiol per day for 3 months, respectively. The sponsor proposed the following indications: 1) moderate to severe vasomotor symptoms and 2) [redacted]

Four main PK studies were conducted to characterize the PK profile of the estradiol acetate vaginal ring. The first study was designed to determine serum estadiol concentrations from [redacted] (0.05 and [redacted] mg/day estradiol) over a 2-week period and from [redacted] (0.1 mg/day estradiol) over a 12 week period (study # HRT 6A or RR 00601). The second study was designed to specifically characterize the Cmax and Tmax of estradiol for [redacted] after 0.1 mg/day product (study # IVR 1001 or RR 00701). The third study was designed to characterize the mutiple-dose PK profile of [redacted] 0.05 mg/day) following administration of two doses: dose 1 for 13 weeks and dose 2 for 4 weeks (study # IVR 1006 or RR 00901). The fourth study was designed for two specific objectives to investigate: 1) the hydrolysis of estradiol acetate and 2) the effect of estradiol on blood coagulation and hemostasis (study # IVR 1005).

Following administration of [redacted] (0.05 mg/day estradiol) for 13 weeks, day 1 serum estradiol concentrations increased rapidly then decreased rapidly to a relatively constant level for three months. Average serum estradiol concentration was about 40 pg/ml. The Tmax and AUC following the two doses were comparable. Following 0.1 mg/day ring for 3 days, serum estradiol level peaked at 1 hour at a concentration of 1665 pg/ml. This was decreased rapidly within 24 to 48 hours postdose (**Figure A**). At 3 months, the average steady state level was about 76 pg/ml. **Figure B** shows estradiol serum concentration-time profiles after administration of 0.05 mg/day rings as two doses on Day 1 and week 13 (study # IVR 1006).

Figure A. Mean (+/-SD) Serum Estradiol (E2) Concentration-Time Profile Following Insertion 0.1 mg/day Vaginal Rings in 12 Postmenopausal Women (Study # IVR 1001)

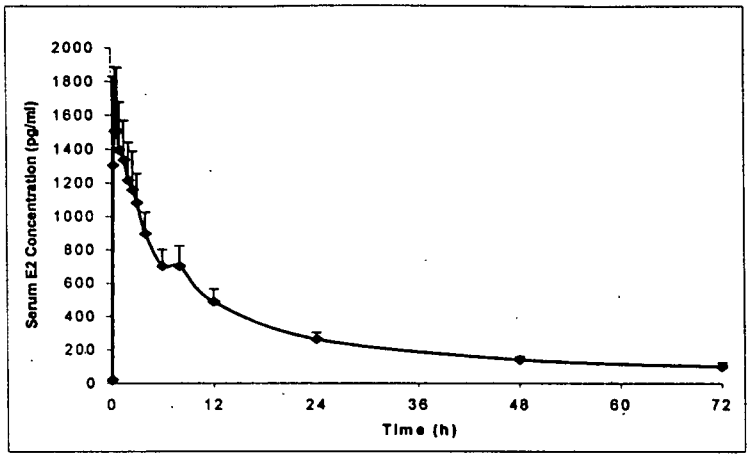
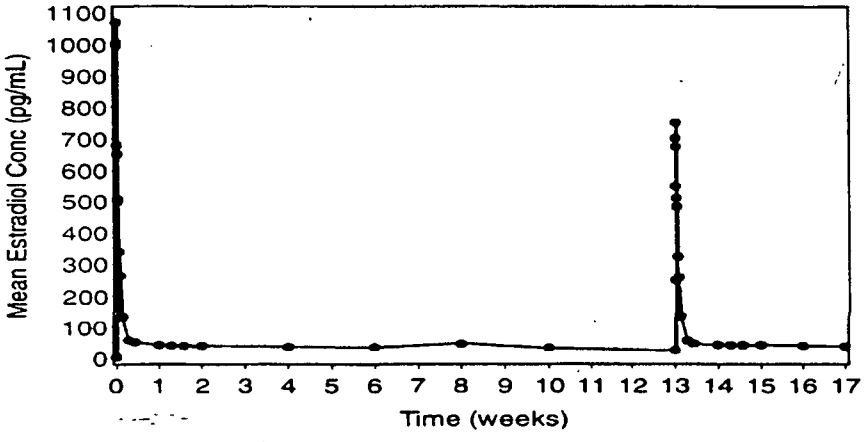


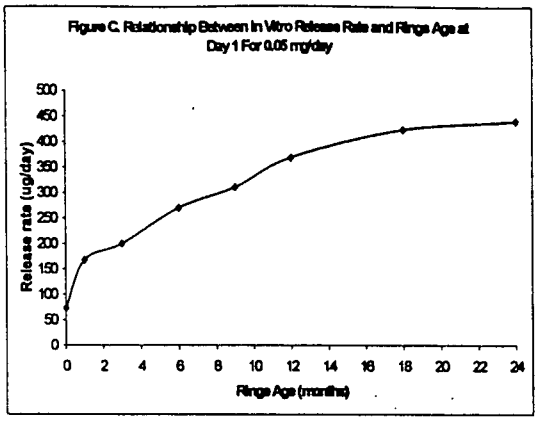
Figure B . Mean serum estradiol concentrations-time profile throughout the study for Dose 1 and Dose 2 of 0.05 mg/day estradiol ring in 25 postmenopausal women (study # IVR 1006).

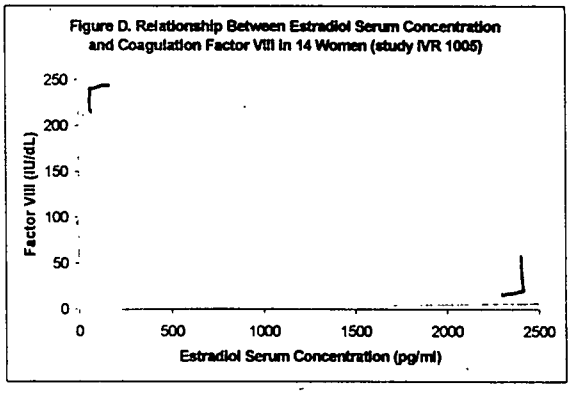


Based on *in vitro* and *in vivo* data, estradiol acetate was very rapidly hydrolyzed/converted to estradiol in serum (study # IVR 1005 or RR 00801). The half-life for the *in vitro* hydrolysis was 28 seconds (study # RR 06801). No estradiol acetate was detected in blood over 72 hours following rings insertion in 14 women (study IVR 1005). Estradiol hydrolysis is catalyzed by esterases, which are found in serum, liver, intestinal mucosa and other tissues.

The two most important questions in this review are: 1) what is the effect of the ring's shelf life (age) on the estradiol release? and 2) what is the clinical consequences of the early and rapid surge of estradiol ? Based on *in vitro* dissolution data, there was increase in estradiol release rate with increasing in rings age (**Figure C**). The early spike in estradiol level does

not appear to be associated with clinically significance effects and specifically on the on coagulation and hemostatic parameters (**Figure D**).





Overall Conclusions:

———— has been developed to deliver estradiol acetate, which is rapidly hydrolyzed to estradiol *in vivo*. Drug delivery from ———— is rapid with peak occurring within the first hour and then declines to a relatively constant rate for 3 months.

There was a rapid surge in estradiol level immediately after intravaginal insertion. The rate of estradiol release from the rings appears to increase with ring's shelf-life (age). There was no obvious relationship between estradiol early surge and any of the hemostatic parameters. In addition, no clinically significant effects were observed in any of the PK studies or in the summary reports of the Phase III studies, irrespective of the rings ages. The rings used in all PK and clinical studies ranged from approximately 17 months to 36 months. The total number of subjects exposed to 36 months old rings was 56 which were as follows: 12, 14, and 30 subjects in the following studies: IVR 1001, IVR 1005, and HRT 8, respectively. These numbers are, in part, based on sponsor's memos/faxes dated August 30 and September 12, 2002.

SUMMARY REVIEW
OF PHARMACOKINETICS AND BIOAVAILABILITY
(Question Based Review, QBR)

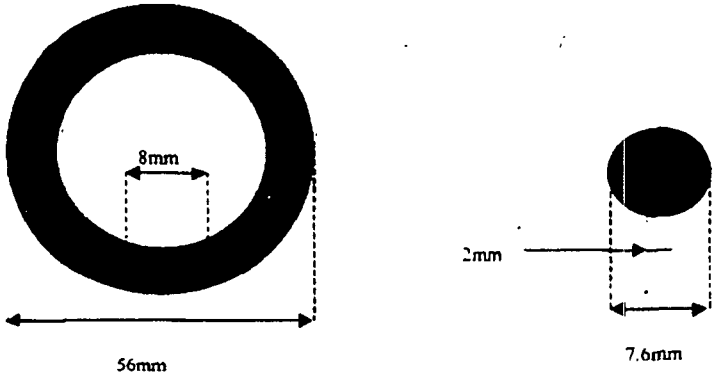
A) BACKGROUND:

What is [ ]?

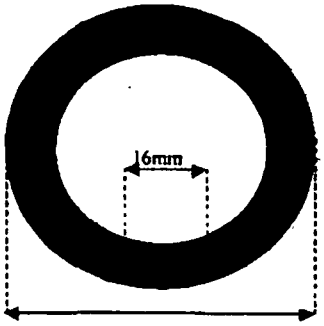
[ ] can also be described as a reservoir system designed to release drug in a controlled and continuous manner for three months. The product can be considered as pro-drug for releasing the parent drug, estradiol, in the systemic circulation. [ ] is a soft and flexible polymer ring that contains a central core of the pro-drug, estradiol acetate. Below are the schematic diagrams of the rings for the two available strengths: 0.05 and 0.1 mg/day (**Figure 1**).

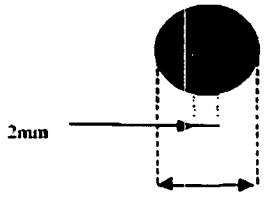
Figure 1. Schematic Diagrams of 0.05 and 0.1 mg/day Rings:

A): [ ]. 0.05 mg/day



B) [ ] 0.1 mg/day





As shown above, _____ is comprised of drug contained in a central core _____ The composition of each type of ring is shown in **Table 1.**

How Estradiol Delivery Rate Was Determined?

The determination of apparent in vivo estradiol delivery rate was determined using the following PK relationship:

CL = Dose/AUC or Dose = CL x AUC, where CL is the clearance.

The daily dose rate was calculated by dividing both sides of the equation by days of treatment. Thus, AUC value divided by days of treatment is average concentration, Cavg.

Therefore, CL X Cavg = daily Dose Rate

The average estradiol clearance reported in the literature is 1280 L/day.

Then (1280 L/day) X Cavg (1000 ml/L) x (1 mg/10^9 pg) = Daily Dose Rate (mg/day)

The following table shows the summary of apparent in vivo delivery rates following administration of estradiol acetate intravaginaly:

Dose (ring size)	Cavg (pg/ml)	Apparent daily Dose Rate
0.05 mg/day	40.6 (study IVR 1006)	0.052 mg/day
0.1 mg/day	76.0 (study HRT 6A)	0.097 mg/day

This method of calculation of the daily delivery rate was faxed by the sponsor on October 9, 2002 and subsequently submitted as amendment to the NDA.

Table 1: Composition of ——————0.05 mg/day and 0.1 mg/day

Component	Function	E3A IVR 0.05mg/day		E3A IVR 0.10mg/day	
		Quantity per Cured Ring (mg)	Quantity per Batch (——→ rings)	Quantity per Cured Ring (mg)	Quantity per Batch —— rings)
(a — cured silicone elastomer, ———					
Elastomer ——					
——	Excipient ——				
Normal Propylorthosilicate	Excipient ——				
Stannous Octoate	Excipient ——				
Total Weight of Elastomer —	-				
——					
—— Composition					
Estradiol Acetate ——	Active (API)	12.4		24.8	
Barium Sulphate, USP	Excipient ——				
Elastomer ——	Excipient ——				
Normal Propylorthosilicate	Excipient ——				
Stannous Octoate	Excipient ——				
Total Weight of ——	-				
Total Weight per Ring	-	7690.00	-	7690.00	-

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What are the Proposed Indications of ————

1) For the treatment of moderate to severe vasomotor symptoms
2) [redacted]

What Are the Process of Formulation Development?

The estradiol acetate ring formulation used in study # IVR 1006 (0.05 mg/day estradiol) was the same formulation studied in the pivotal efficacy trial (study IVR 1002), and it is the market-image formulation. The estradiol acetate vaginal ring (0.1 mg/day estradiol) formulation used in study IVR 1002 differed slightly from the formulations used in the following studies: HRT 6A, HRT 1001, IVR 1005, and HRT 8 (**Table 2**). The difference was in estradiol acetate core length which was —mm used in the PK studies and 16 mm which is to-be-marketed formulation and was also used in the efficacy trial.

Table 2: Formulation Used in Clinical Studies

Study Type	Study No. (Report No)	Dose (as E2 mg/day)	Lot No.	Batch Size	Estradiol Acetate Core Properties			Vaginal Ring Dimensions
					Core Length (mm)	Core Diameter (mm)	Drug Loading (%w/w)	
Pilot PK Studies	HRT 4	0.10	B000459	[redacted]	[redacted]	2.0	[redacted]	[redacted]
		—	B000559					
	HRT 5	—	B001959					
		0.05	B001759			2.0		
		—	B001559					
PK Studies	HRT 6A (RR 00601)	0.05	950902					
		—	950904			2.0		7.6 mm × 56 mm
		0.10	950903					
	IVR 1001 (RR 00701)	0.10	950903			2.0		7.6 mm × 56 mm
	IVR 1005 (RR 00801)	0.10	960902			2.0		7.6 mm × 56 mm
	IVR 1006 (RR 00901)	0.05	99001001		8.0	2.0		7.6 mm × 56 mm
Efficacy Studies	HRT 8 (RR 01401)	0.05	960901		—	2.0		7.6 mm × 56 mm
		0.10	960902		—	2.0		7.6 mm × 56 mm
	IVR 1002 (RR 01101 RR 01901)	0.05	99001001		8.0	2.0		7.6 mm × 56 mm
		0.10	99002001		16.0	2.0		7.6 mm × 56 mm

Is There Any Difference in the *in vitro* Dissolution Profiles Between the — mm and the 16 mm Core Length Rings?

To assess the impact of the small difference in core length on the delivery rate, the similarity factor (f2) was determined for the — mm (lot # 950903) and the 16 mm (lot # 99002001) core length (**Table 2**). The similarity factor (f2) was 81.3 which is between 50 and 100. This indicates no difference between the two formulations. **Figure 1** shows the cumulative dissolution profiles for both formulations. **Tables 3 and 4** show the dissolution method specifications for 0.05 and 0.1 mg/day rings. It should be noted that both sizes were used in the efficacy studies # HRT 8 and IVR 1002 (**Table 2**). For further details, please also see the CMC/chemistry review for this NDA.

Figure 1. Cumulative *in vitro* dissolution profiles for — mm and 16 mm rings for 0.1 mg/day formulations

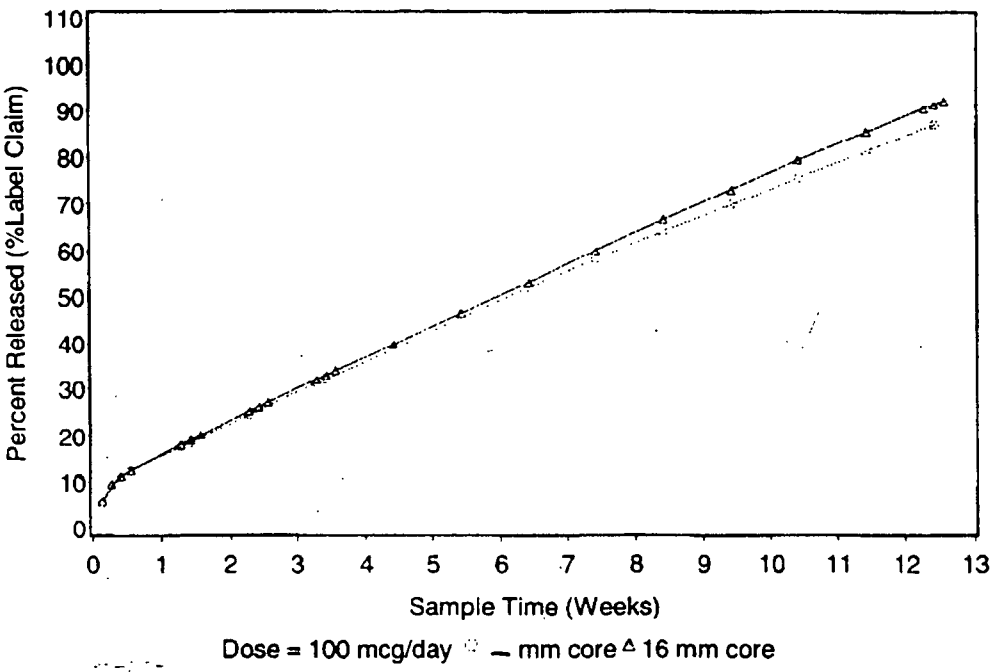

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Table 3. Specification and Test Methods for [redacted] 0.05 mg/day Rings (Formulation # IVR/FP/017-1)

Apparatus: [redacted]
Speed: [redacted]
Media: [redacted]
Volume: [redacted]
Sampling Time: [redacted]
Analytical method: Hydrolyzed estradiol acetate to estradiol, quantify estradiol by [redacted]

TEST	SPECIFICATION	METHOD DESCRIPTION
DISSOLUTION [redacted]	[redacted]	Dissolution. [redacted]

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Table 4. Specification and Test Methods for [redacted] 0.1 mg/day Rings (Formulation # IVR/FP/018-1)

Apparatus: [redacted]
Speed: [redacted]
Media: [redacted]
Volume: [redacted]
Sampling Time: [redacted]
Analytical method: Hydrolyzed estradiol acetate to estradiol, quantify estradiol by [redacted]

TEST	SPECIFICATION	METHOD DESCRIPTION
DISSOLUTION [redacted]	[redacted]	Dissolution. [redacted]

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What is the Effect of Shelf Life (Ring's Age) on *in vitro* Release of Estradiol?

Based on *in vitro* data, there was an increase in estradiol release with age of the ring tested up to 24 months (**Figures 2-3**). The rate of release starts to reach the plateau by 12 months. In addition, the *in vitro* data show a rapid and sharp release of estradiol on Day 1 followed by a rapid drop in estradiol release for all rings, regardless of the age. The data presented in these figures are for 0.05 mg/day rings only. The same trend was also seen for 0.1 mg/day rings. Furthermore, it should be noted that this data was collected at a temperature of 25°C. Additional, but incomplete, data are also available at 40°C temperature with slightly higher rate of release. The trend in the release rates was the same, irrespective of the temperatures.

Note: The data on day 2, 3, and 4 were not submitted in the original NDA, but were acquired during the manufacturing site inspection by Dr. Jean Salemme (see CMC and chemistry review by Dr. Salemme).

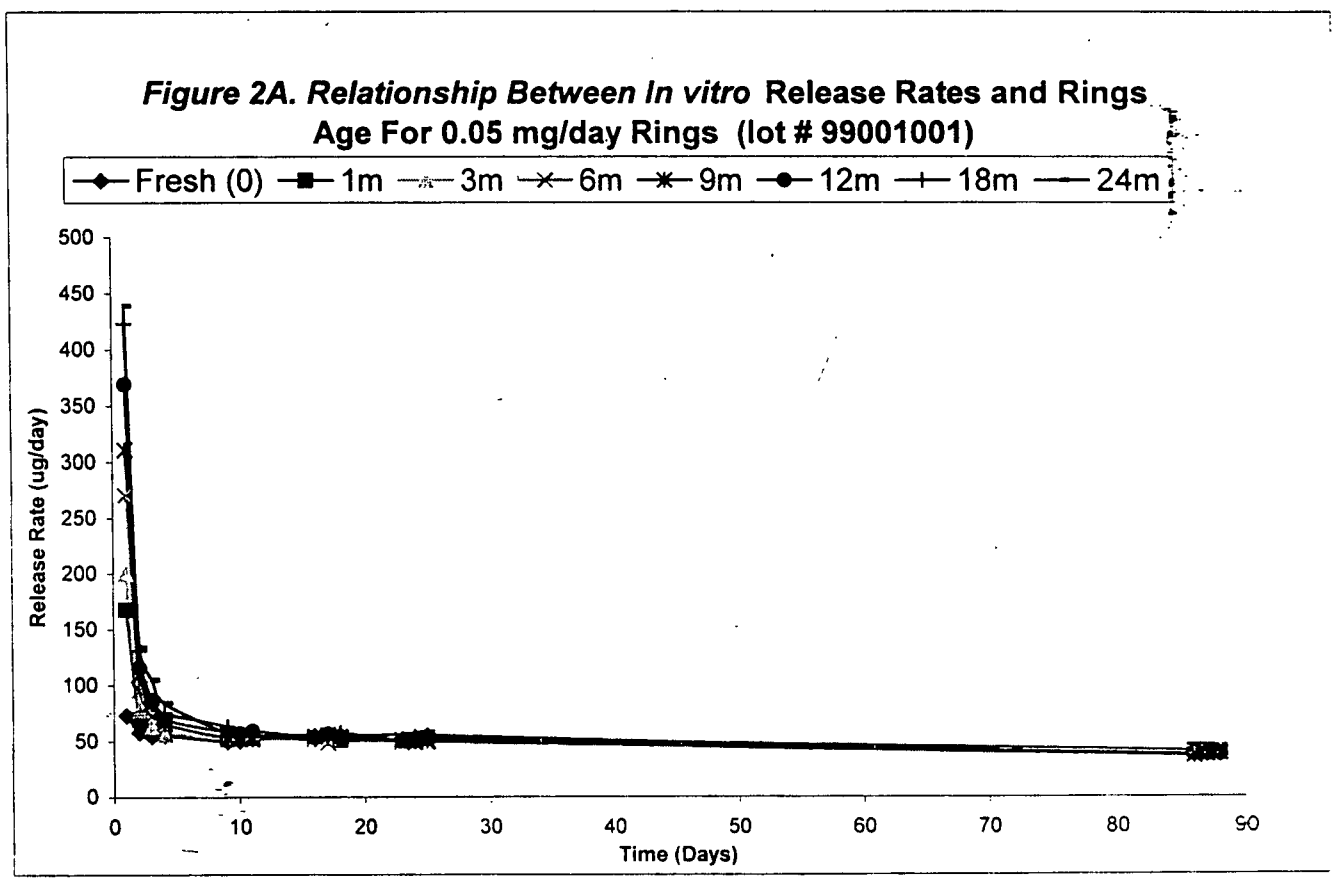

Figure 2B. Relationship Between in Vitro Release Rates Up To 10 Bays and Rings Age For 0.05 mg/day Rings (Lot# 99001001)

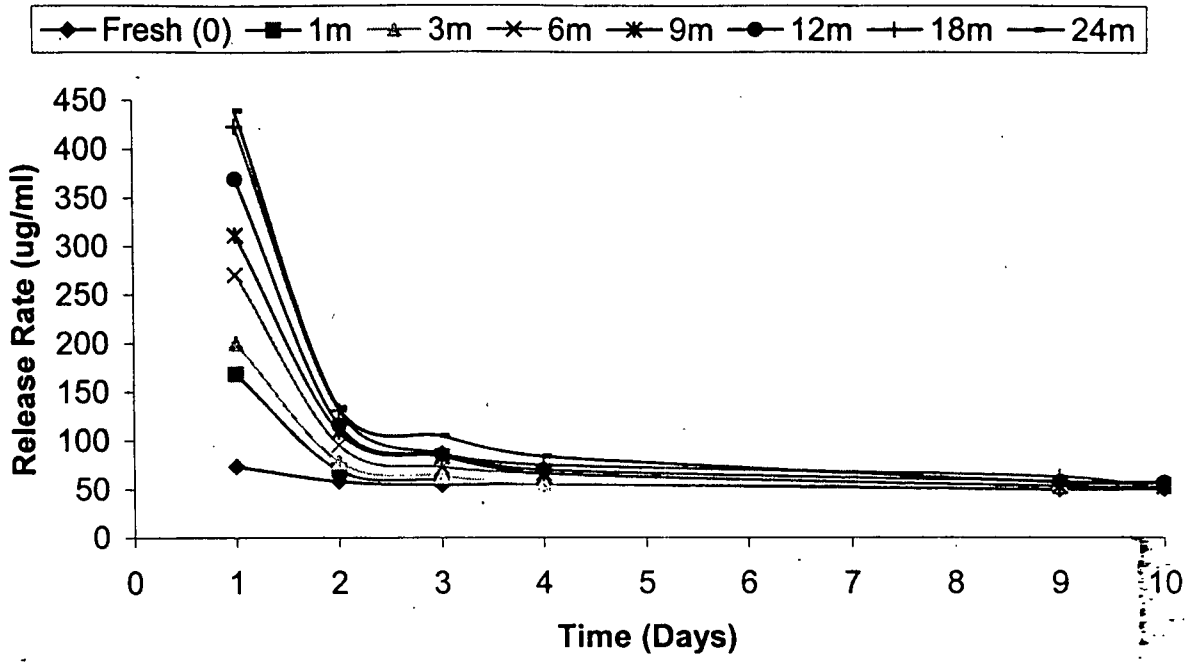

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Figure 3. Relationship Between *in Vitro* Release Rate and Rings Age at Day 1 For 0.05 mg/day

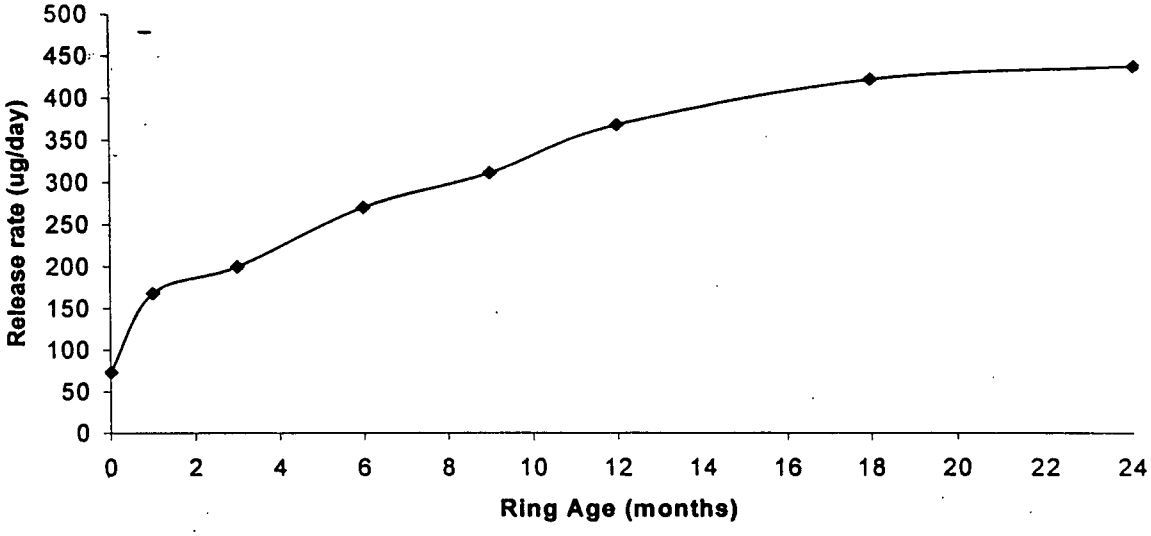

Table 5 shows mean estradiol concentration released in — media from 36 months old 0.5 mg/day ring on Day 1 was 586.6 µg/day and on Week 2,3, and 4 was 96.7 µg/day. This particular lot (36 months old) was used in the clinical study HRT-8. In this study, a total of 30 subjects were exposed to this 36 months old ring. No clinically significant adverse events were noted using these formulations (see also clinical trail section of this review).
Additional data were submitted by the sponsor on September 23, 2002 as amendment # 12 to the CMC section of the NDA. The table below show the release rates on day 1 for the batches used in two clinical studies: IVR 1002 and 1006.

Mean Estradiol Release Rates (µg/day) of All Rings For Day 1 (data from Appendix 10. Tables 1 and 4, CMC Amendment Dated September 23, 2002)

			Time Points (months)			
Study #	Rings	Batch #	12	18	24	36
IVR 1002	0.05	99001001	369.1	422.9	439.1	456.0
IVR 1006	0.1	99002001	437.3	513	522.5	527.2

For further details on *in vitro* performance and shelf-life/stability data, please refer to the CMC /chemistry review.

It should be noted that there were two speeds in the data presented in **Table 5**. The sponsor stated that during the course of development the — and dissolution medium changed from — rpm and from — solution to — solution, respectively (sponsor's fax dated August 23, 2002). Another difference between the test methods was that Day 1 release rate was not determined in the — method. In cases where the dissolution study for release testing was performed only in — available data in — was also provided. A description of the — dissolution method and specifications

for both formulations are shown in **Tables 3 and 4.**

Table 5: Effect of Shelf-Life/Ring's Age on the *in Vitro* Release Data

Dose (mg/day E2)	Study No.	Lot Number	[redacted]	Media	IVR age (months)	Sample Time	Mean (µg/day)	n
0.05	HRT 6A	950902			0	Week 2,3,4	68.3	5
					29	Day 1	419.6	3
						Week 2,3,4	49.1	3
—	HRT 6A	950904			0	Week 2,3,4	99.0	5
0.10	HRT 6A IVR 1001	950903			0	Week 2,3,4	126.3	5
					29	Day 1	486.0	3
						Week 2,3,4	85.9	3
0.05	HRT 8	960901			0	Week 2,3,4	61.4	10
					17	Day 1	306.0	3
						Week 2,3,4	49.7	3
0.10	IVR 1005 HRT 8	960902			0	Week 2,3,4	108.4	9
					36	Day 1	586.6	6
						Week 2,3,4	96.7	6
0.05	IVR 1002 IVR 1006	99001001			0	Day 1	73.3	5
						Week 2,3,4	52.9	5
0.10	IVR 1002	99002001			0	Day 1	142.6	5
						Week 2,3,4	90.6	5

Does Estradiol Acetate Hydrolyzed *in vitro*?

Study RR 06801 was conducted to investigate the *in vitro* hydrolysis of estradiol acetate. Estradiol acetate was incubated at 37°C in human serum at a concentrations of 500, 2000, and 5000 pg/ml and at 5000 pg/ml in whole blood. Serial blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 5, and 10 minutes after spiking estradiol acetate in the matrix (serum or whole blood). Samples were immediately treated with ethyl acetate to terminate any further esterase reactions. All samples were analyzed by [redacted] method for estradiol acetate and estradiol.

Results:

There was a rapid hydrolysis of estradiol acetate with a half-life of 28 seconds (**Figure 4 and Table 6**).

Figure 4. ***In vitro*** **serum estradiol acetate concentrations as a function of time at the starting concentrations of 500, 2000 and 5000 pg/ml. Each experiment was in triplicate (study # RR 0680).**

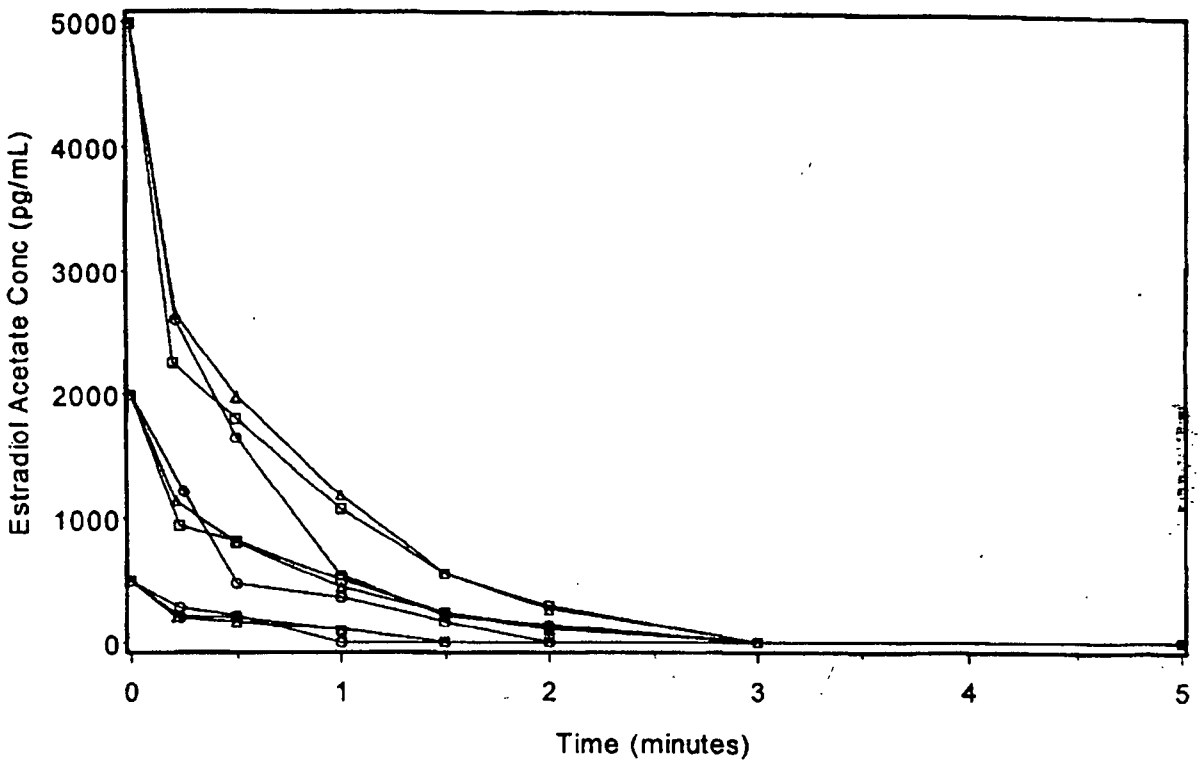

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Table 6. Summary of hydrolysis rate constant values (study # 0680)

Initial Estradiol Acetate Concentration (pg/mL)	Trial Number	k_1 (1/minute)	t ½ (minutes)	t ½ (seconds)
500	A3	-1.67	0.41	24.8
2000	A3	-1.59	0.43	26.1
5000	A3	-1.83	0.38	22.7
500	A5	-1.43	0.49	29.1
2000	A5	-1.32	0.52	31.4
5000	A5	-1.37	0.50	30.3
500	A6	-1.43	0.49	29.1
2000	A6	-1.36	0.51	30.6
5000	A6	-1.29	0.54	32.3
Mean		-1.48		
SD		0.18		
%RSD		12.4		
N		9		

k_1 = first order rate constant for estradiol acetate hydrolysis (1/minute)
t ½ = hydrolysis half-life (minutes)

Conclusion:

Based on this data, within <5 minutes all estradiol acetate is completely hydrolyzed by blood esterase to estradiol. Therefore, no estradiol acetate is expected to be found *in vivo* (see also **in vivo** study # IVR 1005).

Does Estradiol Acetate Hydrolyzed *in vivo*?

Study IVR 1005 was conducted to investigate the conversion of estradiol acetate to estradiol after ring insertion. In this study, 0.1 mg/day rings were inserted intravaginally to14 women. Blood samples were collected at pre-dose, 5, 15, 30, and 45 minutes and 1, 1.5, 24, and 72 hours after rings insertion.

It should be noted that estradiol acetate was measured only in whole blood, whereas estradiol was measured in both whole blood and serum. The whole blood was inadequate biological matrix for measurement of estradiol and estradiol acetate.

Conclusion:

Based on this study, estradiol acetate was not detected in any of whole blood samples collected during this study. There was no clinically significant effects observed in this study. The rings used in this study were 36 months old. See the next section on the effect of rings shelf-life (age) on estradiol release.

Is There Any Clinical Significance of the Early Surge in Estradiol Serum Concentration?

This is an important question that needs to be addressed. In all clinical pharmacology and PK studies submitted and reviewed in this NDA, there was immediate surge of estradiol serum level reaching a concentration of about 2000 pg/ml or higher in some situations (see below). In all studies, serum estradiol drops to approximately 50-100 pg/ml within the first two weeks and prior to the insertion of the next ring. [redacted] is proposed to be inserted once every 3 months. From the available *in vitro* data and also some clinical data, the surge in estradiol level with aged rings ranging from 17 to 36 months (**Table 5**) does not seem to affect the performance of the release when administered to women. As stated above, based on *in vitro* data the surge in estradiol level appears to be higher with older rings compared to fresh rings (**Figures 2 A&B and 3 and Table 5**). Since there is an immediate and rapid decline in estradiol level following insertion and prior to the insertion of the next ring, the clinical significance of this surge may not be of great concern.

As described earlier, study IVR 1005 was designed mainly to investigate the *in vivo* hydrolysis of estradiol acetate. In this study, 0.1 mg/day rings were inserted intravaginally in 14 women. The rings used in this study were 36 months old. The second objective of this study was to monitoring the effect of the early spike in estradiol serum level on hemostasis. A series of blood samples were collected at pre-dose, 15, 30, 45, and 60 minutes and 24 and 72 hours after rings insertion.). It is noteworthy that the hemostasis data were collected within the first hour of insertion and then at 24 hours and 72 hours. Therefore, no data are available between 1 hour and 24 hours.

The mean coagulation and hemostasis parameters are shown in **Figures 3-10A-D and Tables 7-11**. Examining the individual data there was no obvious change or relationship between estradiol serum level and any of the hemostasis parameter and in particular the coagulation factor VIII and the thrombin-antithrombin complex (TAT-**Figures 3-10A-D**). On October 1, 2002 the sponsor submitted additional analysis to establish the PK/PD relationship between hemostatic parameters and estradiol serum levels. There was no realtionship estradiol serum level and any of the hemostatic parameters. For example, **Figures C and D** shows show the relationship between estradiol serum levels and Factor VIII and TAT, respectively.

It should be noted that there was some variability in the data and a few outliers that were excluded from the analysis. Overall, most of the hemostasis data were within the normal range with a few exceptions. For examples, there was slight increase in the mean values of Factor VIII at 15 min, 24, and 72 hours (**Table 7**). In addition, the mean thrombin-antithrombin complex (TAT) value at 30 min was more than twice higher than the baseline value (**Table 8**). This increase in factor VIII and TAT values corresponds to the time of Cmax of estradiol serum level which is <1 hours (**Table 12 and Figure 11**). The mean (± SD) of Cmax was 1502 ± 451 pg/ml ranging from 940 to 2247 pg/ml. The mean (± SD) of Tmax was 0.98 ± 0.5 h ranging from 0.5 to 1.5 hour (**Table 12**). Furthermore, there was a good correlation between *in vitro* estradiol release rate and *in vivo* performance for the same rings used in study IVR 1005 (Lot # 960902, **Figures 11 and 12**). Both *in vitro* and *in vivo*

data show a rapid rate of release of estradiol followed by a rapid drop.

General Comments:

There was no clinically significant adverse events noted in any of the PK studies nor in the summary reports of the clinical studies (see also the medical and the safety review).

Estradiol is well known drug with tremendous clinical history. The surge in estradiol level is short-lived and has not been shown to be associated with a major clinical or safety issue. Theoretically, some patients with certain diseases (e.g., cardiovascular) may not tolerate the rapid surge of estradiol. In study IVR 1005, the surge in estradiol level had little if no effect on hemostasis parameters. The changes in the mean values of some of the hemostasis parameters were transient and short lived **(Tables7-11 and Figures 3-10A-D)**

Some patients with cardiovascular complications may need to be monitored carefully during the burst in estradiol level. A cautionary statement in reference to estradiol surge in certain patients during the first week of ring's insertion should be included in the label. As noted above based on both *in vitro* and *in vivo* data, the surge is higher in older rings than fresh rings. However, the use of the 36 months old rings in 30 subjects in Phase III trail (HRT 8) did not show any clinically unusual adverse events. For further discussion on the safety of this product, please see the Medical Officer's review.

Conclusions:

Apart from a transient changes in some of the homostasis parameters, no other changes were found during the 72 hours study (study # UVR 1005). Specifically, no major changes were found during the time of surge in estradiol serum concentration.

Figure 3. Relationship Between Estradiol Serum Concentration and Coagulation Factor VIII in 14 Women (study IVR 1005)

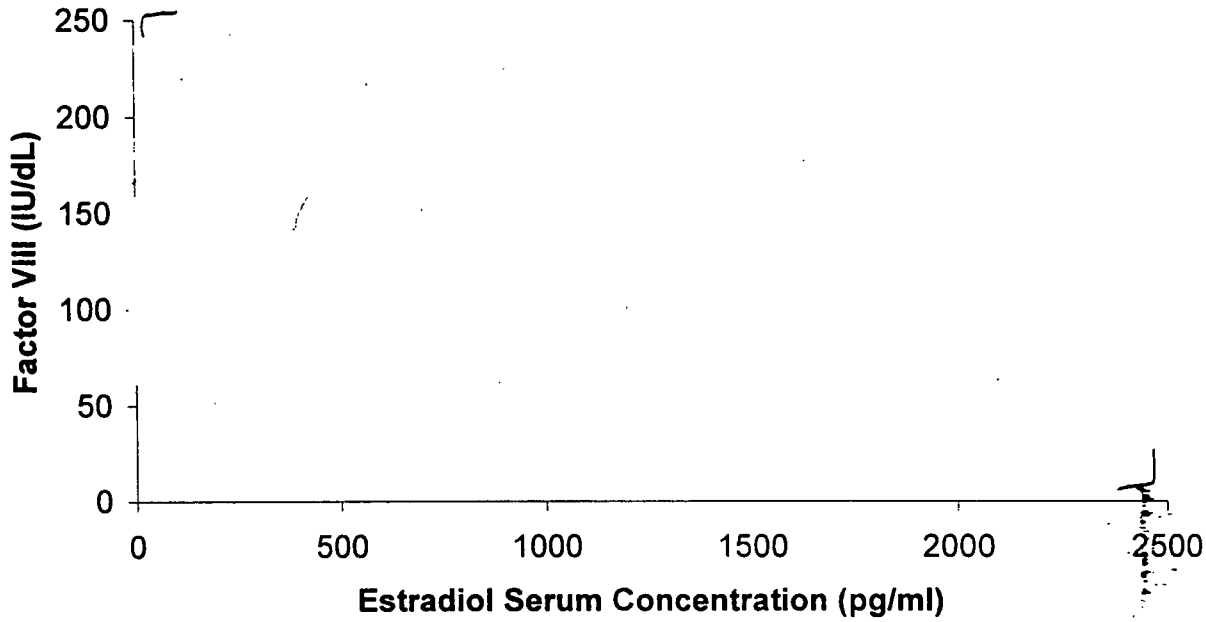

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Figure 4. Individual Concentration for Coagulation Factor VII (study IVR 1005)

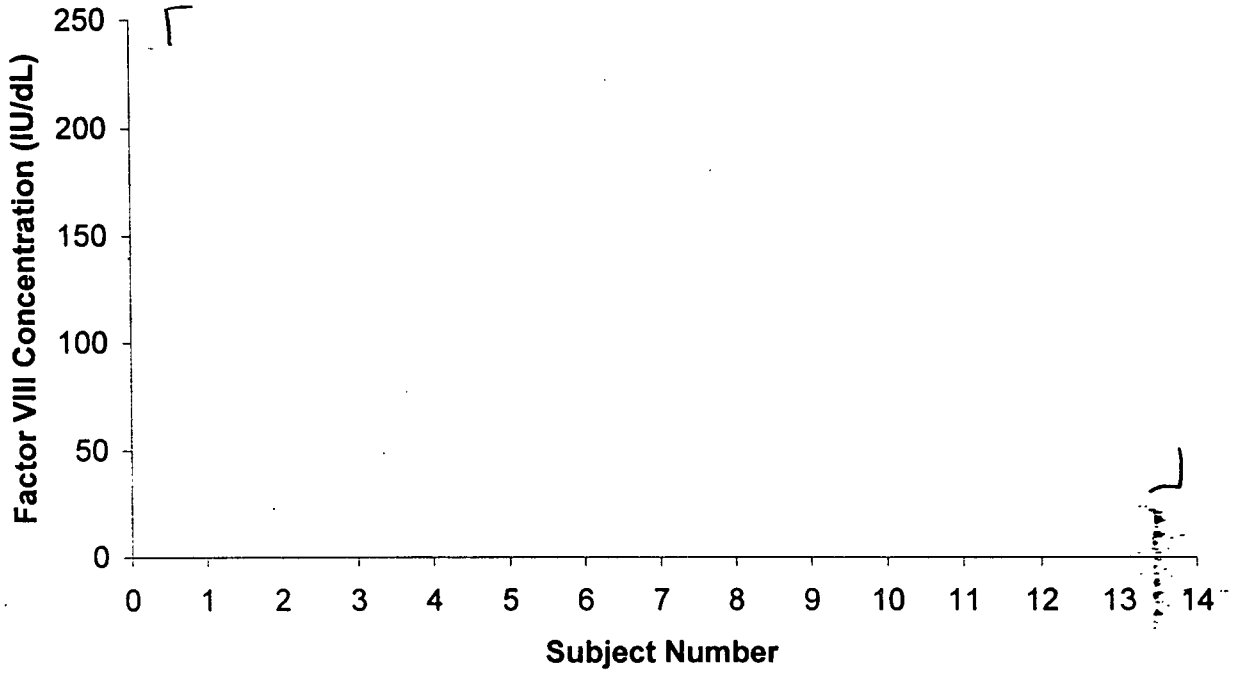

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Figure 5. Individual Coagulation Factor VIII Concentration - Time Profiles During First Hour (study IVR 1005)

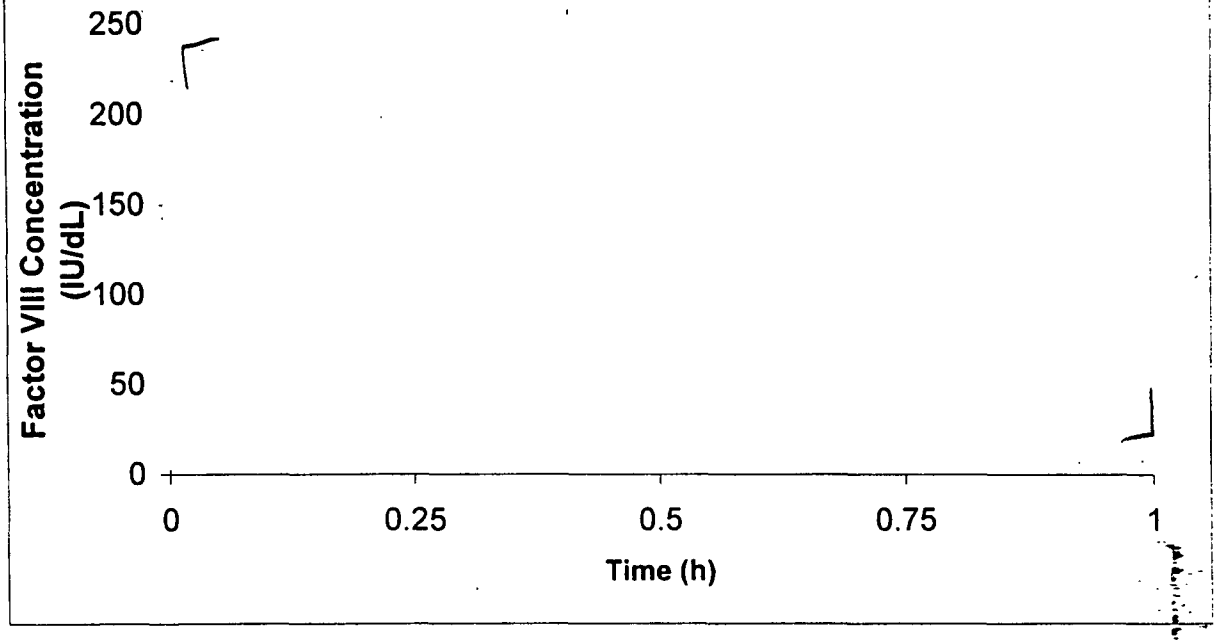

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Figure 6. Individual Coagulation Factor VII Concentration-Time Profiles Over 72 hours (Study IVR 1005)

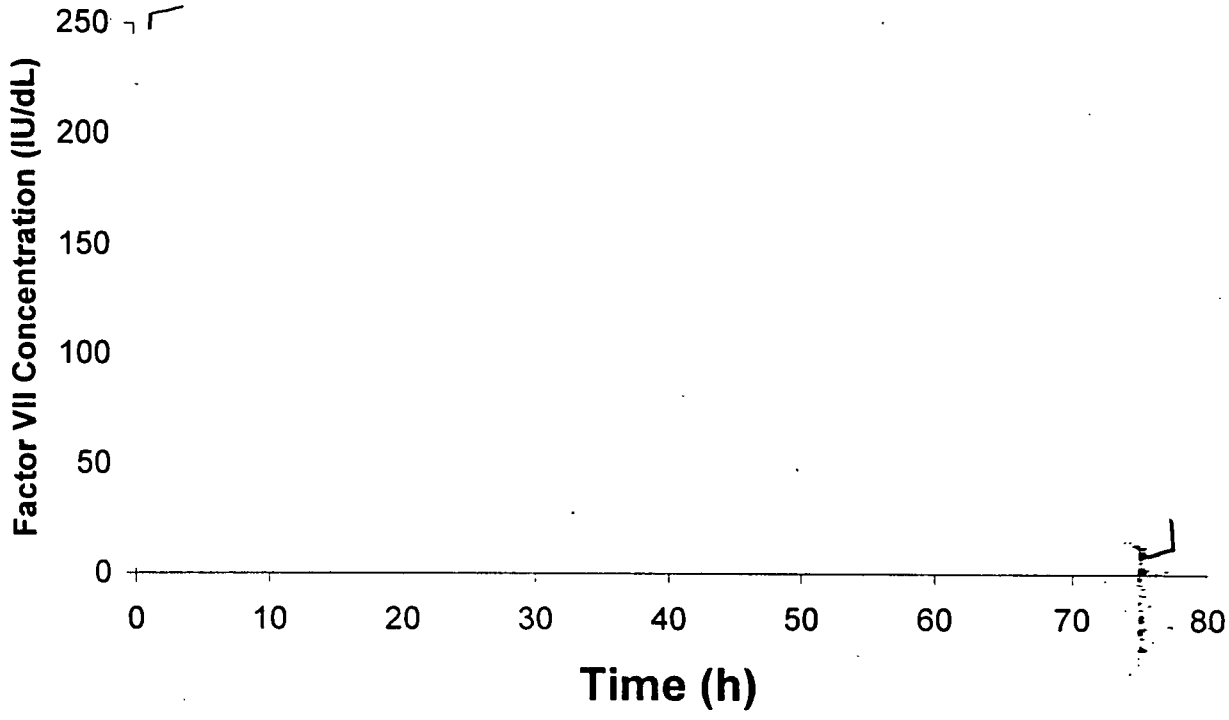

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Figure 7. Relationship Between Estradiol Serum Concentration and Thrombin-Antithrombin Complex (TAT) in 14 Women (Study IVR 1005)

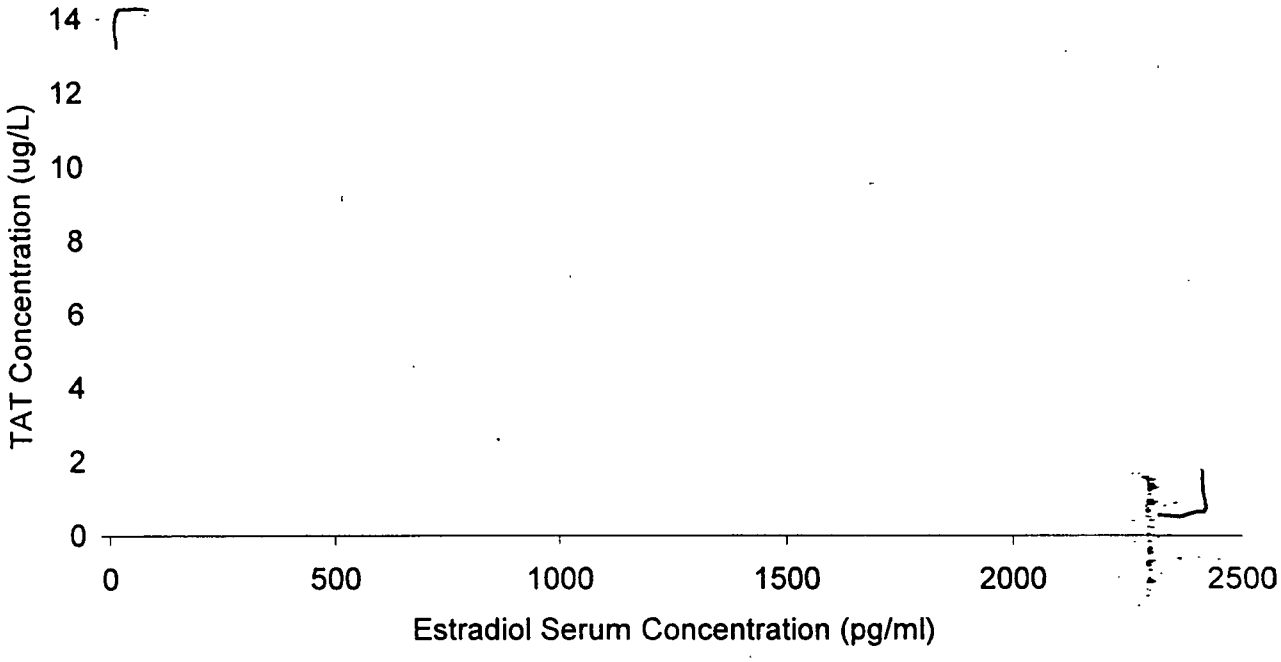

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Figure 8. Individual Thrombin-Antithrombin Complex (TAT) Concentrations (Study IVR 1005)

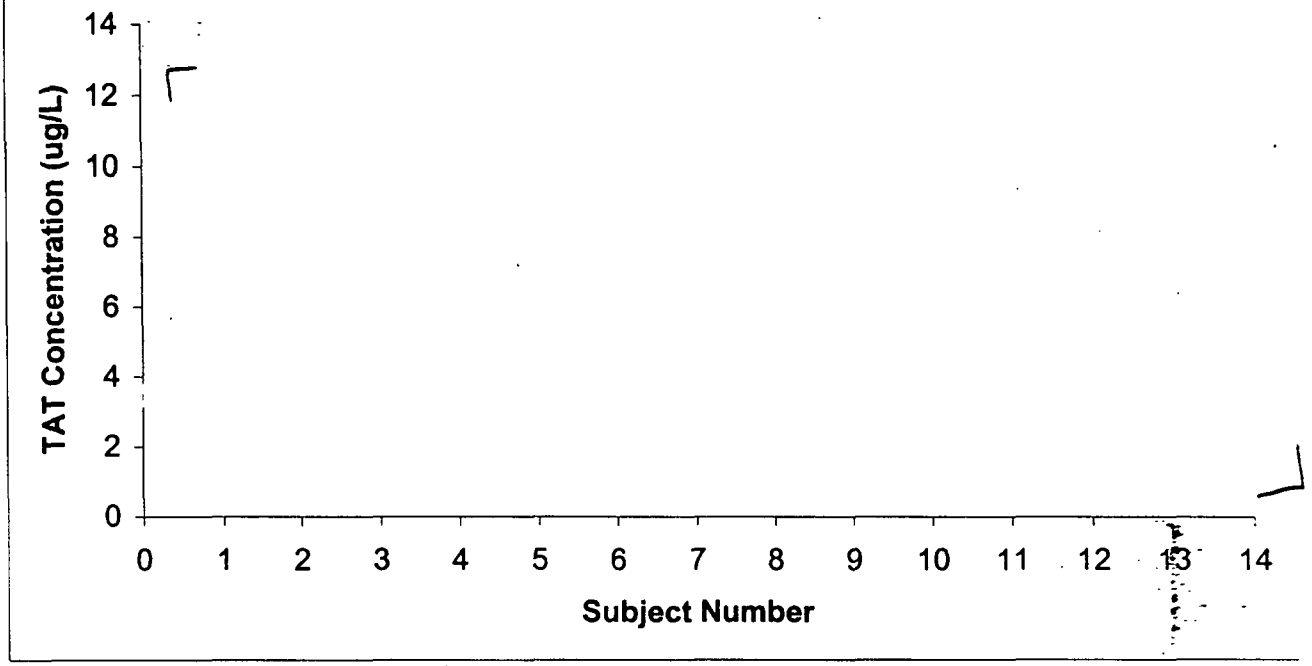

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Figure 9. Individual Coagulation Factor VIII Concentration - Time Profiles During First Hour (study IVR 1005)

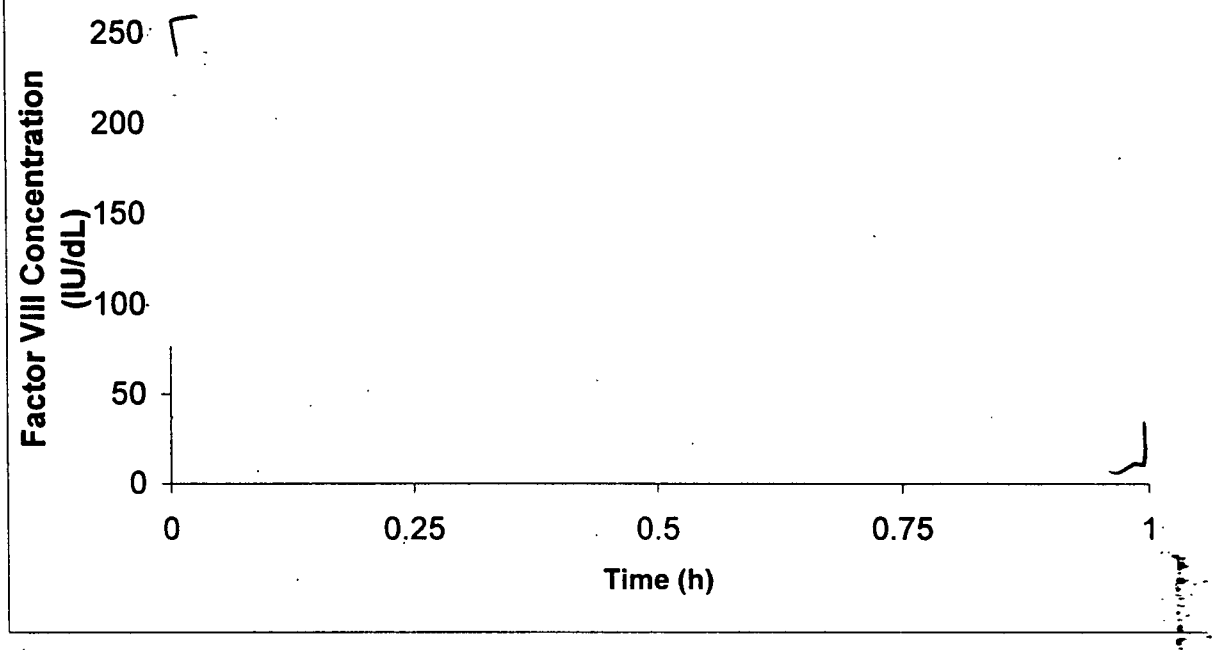

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Figure 10A. Individual Thrombin-antithrombin Complex (TAT) Concentration-Time Profiles over 72 hours (Study IVR 1005)

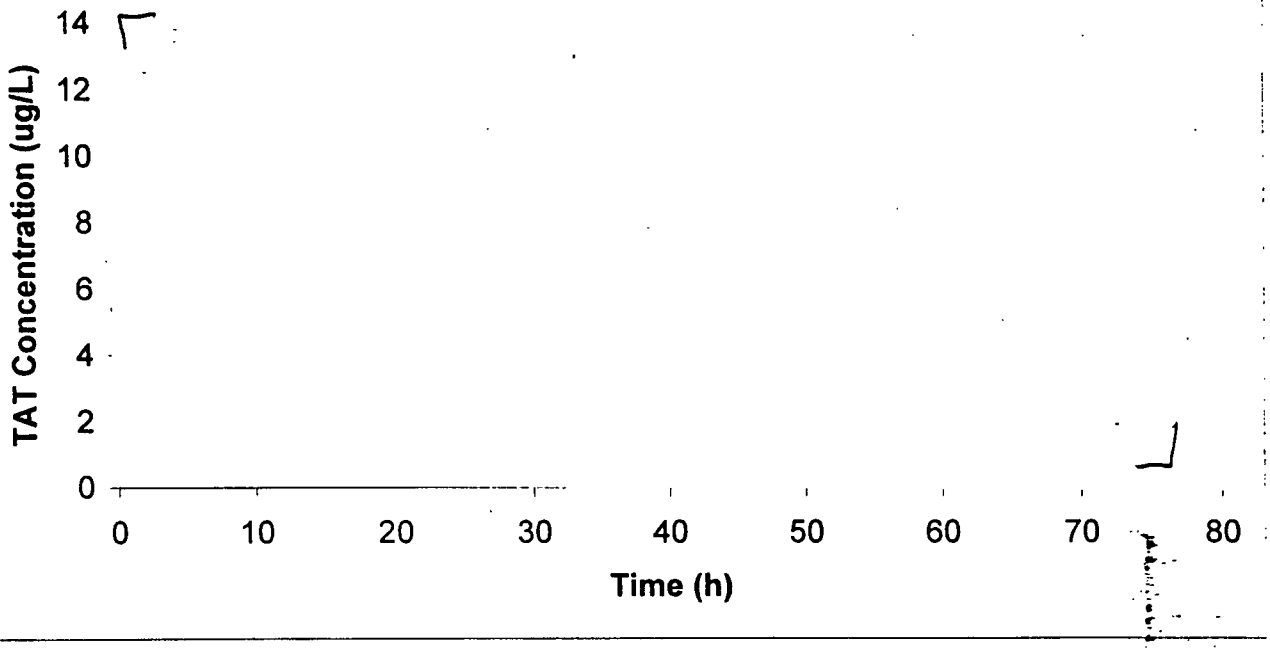

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Figure 10B. Individual TAT Concentration-Time Profiles During the First Hour (study IVR 1005)

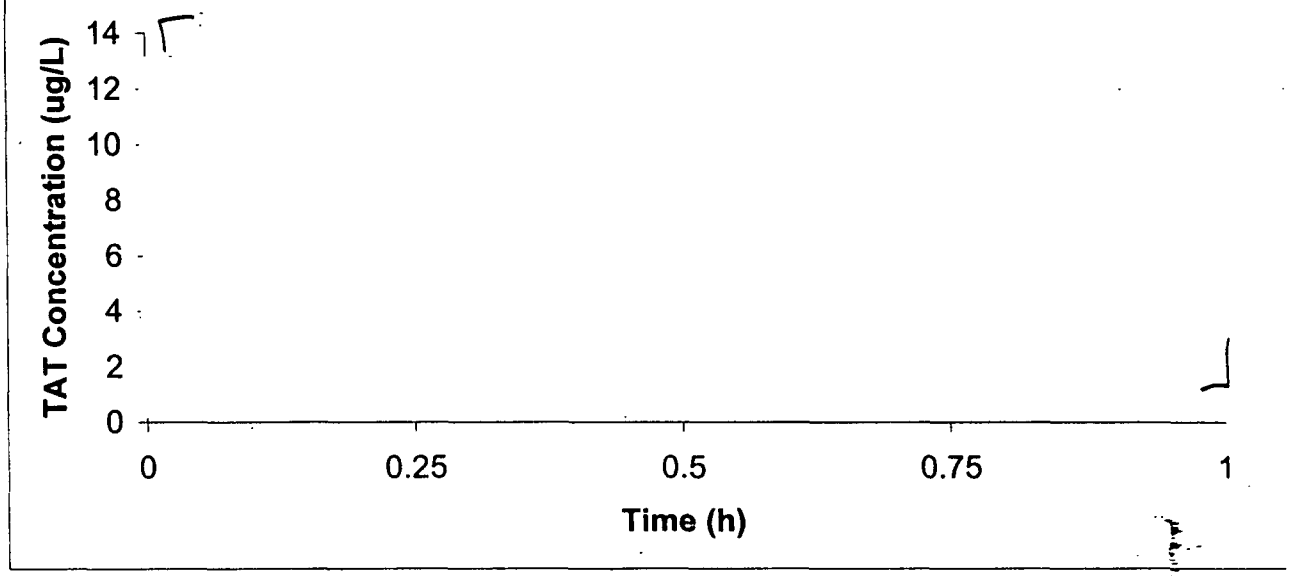

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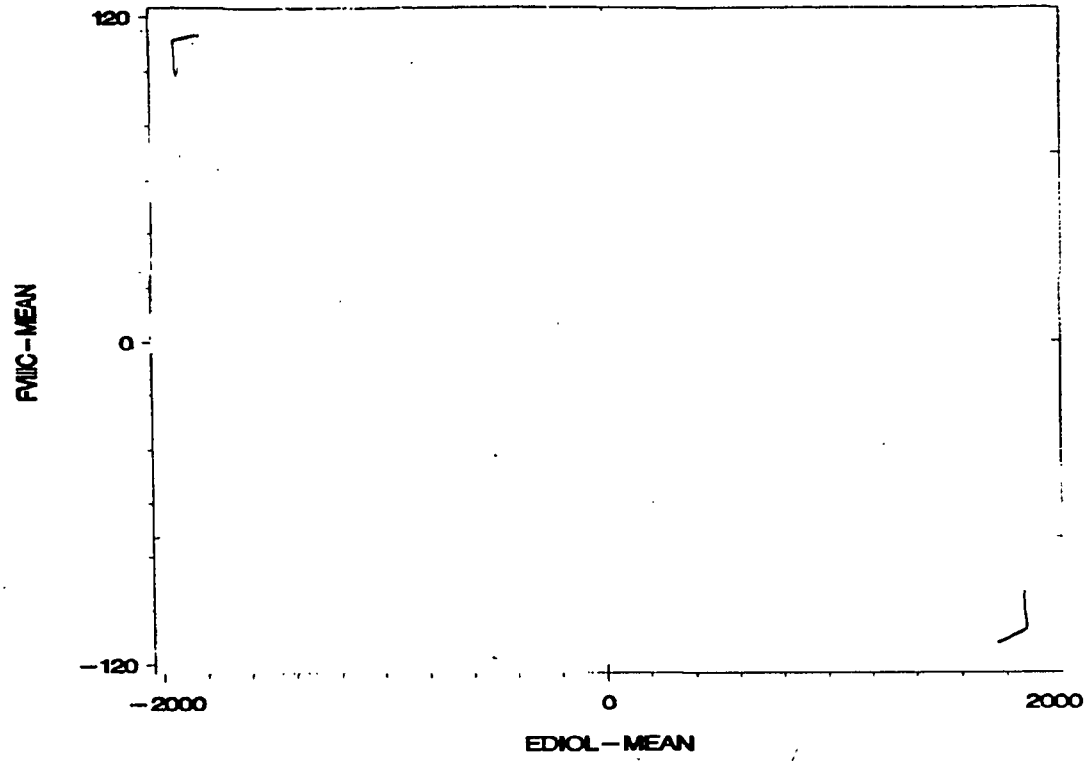
Figure 10C: Sponsor's Scattered Plot for the Relationship Between Factor VIII and Estradiol Concentration. Open Circle from Study IVR 1005 and Closed Circle from Study IVR 1006. Data Submitted on October 1, 2002.



Frequency Counts by Quadrant

ED\FVIIIC	<Mean	>=Mean
>=Mean	90, 30%	48, 16%
<Mean	112, 37%	52, 17%

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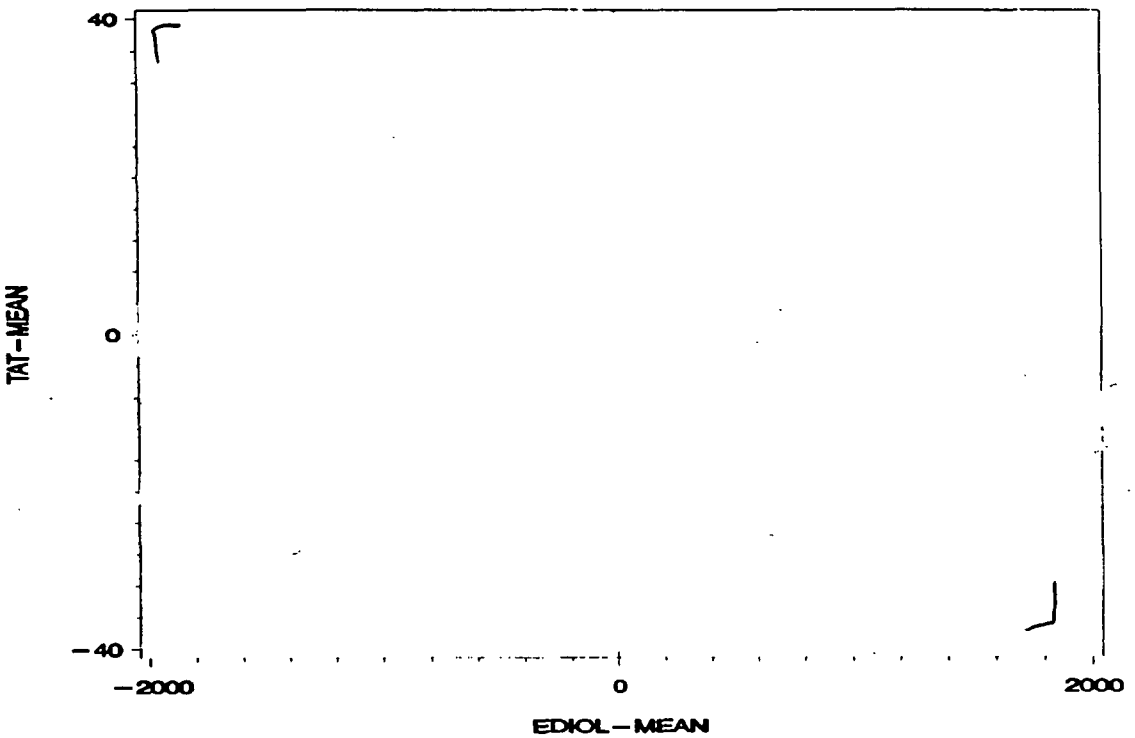
Figure 10D: Sponsor's Scattered Plot for the Relationship Between TAT and Estradiol Concentration. Open Circle from Study IVR 1005 and Closed Circle from Study IVR 1006. Data Submitted on October 1, 2002.



Frequency Counts by Quadrant

ED\FVIIIC	<Mean	>=Mean
>=Mean	19, 6%	15, 5%
<Mean	183, 61%	85, 28%

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Table 7: Mean (± SD) Factor VIII Coagulation Activity (study IVR 1005):

n=13 [a]	Mean (IU/dL)	SD
Baseline (0 min)	150	31.8
15 min	156 *	33.5
30 min [b]	150	33.4
45 min	149	37.8
60 min	152	33.1
24 h	168 *	29.0
72 h	169 *	26.2

Reference range: 46–189 IU/dL
[a] The blood sample from Subject 10 was hemolyzed so results were not included
[b] n=12: a missing sample was reported for Subject 14 at 30 min
* Change from Baseline significant at a level of $p < 0.05$

Table 8. Phrombin-Antithrombin Complex (Study IVR 1005)

n=13 [a]	Mean (µg/L)	SD
Baseline (0 min)	3.51	2.28
15 min	4.64	3.05
30 min [b]	8.92	17.10
45 min	4.59	3.21
60 min	4.05	2.31
24 h	4.34	4.87
72 h	1.46 *	1.34

Reference range: 1.0–4.1 µg/L
[a] The blood sample from Subject 10 was hemolyzed so results were not included
[b] n=12; a missing sample was reported for Subject 14 at 30 min
* Change from Baseline significant at a level of $p < 0.05$

Table 9. Prothrombin Fragment 1 and 2 (Study IVR 1005)

n=13 [a]	Mean (nmol/L)	SD
Baseline (0 min)	0.96	0.38
15 min	0.91	0.35
30 min [b]	0.91	0.38
45 min	0.90	0.38
60 min	0.92	0.37
24 h	1.02	0.64
72 h	0.87	0.35

Reference range: 0.4–1.1 nmol/L
[a] The blood sample from Subject 10 was hemolyzed so results were not included
[b] n=12; a missing sample was reported for Subject 14 at 30 min

Table 10: Mean (± SD) von Willebrand Factor Antigen (study IVR 1005):

n=13 [a]	Mean (IU/dL)	SD
Baseline (0 min)	116	27.7
15 min	121	34.7
30 min [b]	111	28.9
45 min	115	29.6
60 min	114	29.4
24 h	132 *	35.0
72 h	130 *	29.3

Reference range: 50–200 IU/dL

[a] The blood sample from Subject 10 was hemolyzed so results were not included

[b] n=12; a missing sample was reported for Subject 14 at 30 min

* Change from Baseline significant at a level of $p < 0.05$

Table 11. Free protein S and Total Protein S (Study IVR 1005)

	Free Protein S		Total Protein S	
n=13[a]	Mean (IU/dL)	SD	Mean (IU/dL)	SD
Baseline (0 min)	101	16.8	97	16.8
15 min	100	15.0	96	19.2
30 min[b]	104	24.8	103	18.8
45 min	100	17.1	99	13.6
60 min	101	14.9	96	9.3
24 h	95	15.2	96	14.5
72 h	98	21.5	96	16.4

[a] The blood sample from Subject 10 was hemolyzed so results were not included

[b] n=12; a missing sample was reported for Subject 14 at 30 min

Reference range: 51–140 IU/dL Reference range: 64–166 IU/dL

Table 12. Serum Estradiol PK Parameters (Study IVR 1005)

Subject	Cmax (pg/mL)	tmax (h)	AUC(0–72) (pg·h/mL)
01	1724.3	0.75	27626.4
02	2023.0	0.75	40790.5
03	1683.5	1.00	33846.8
04	1437.8	1.00	27010.1
05	940.4*	1.50*	20203.8
06	2027.1	0.50	26117.8
07	1466.7	0.50	24282.1
08	1343.4*	1.50*	27066.6
09	1389.3*	1.50*	26480.5
10	1040.6	1.00	20446.5
11	1899.2	0.25	28319.0
12	2246.6	0.50	31069.6
13	833.5*	1.50*	21210.5
14	970.8*	1.50*	23948.5
Mean	1501.9	0.98	27029.9
SD	450.8	0.5	5520.2
%RSD	30	46.3	20.4
n	14	14	14

Figure 11. Mean Serum Estradiol Concentration-Time profile Over 72 Hours in 13 Women (Study IVR 1005)

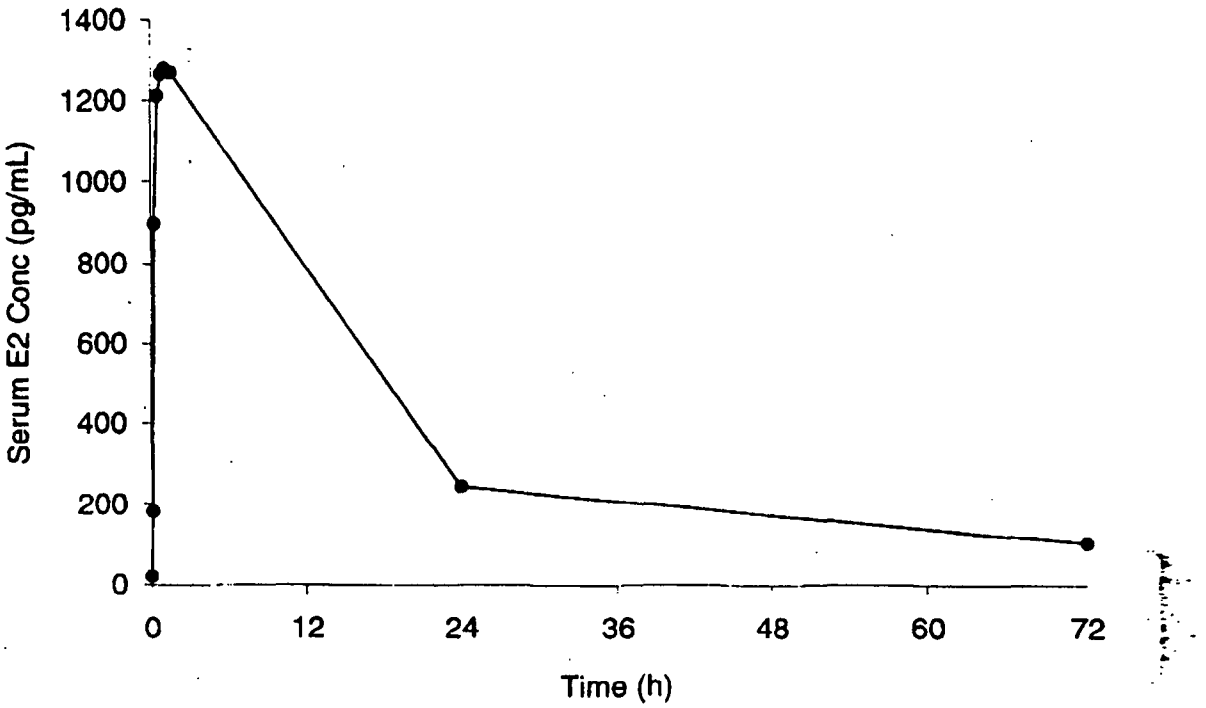
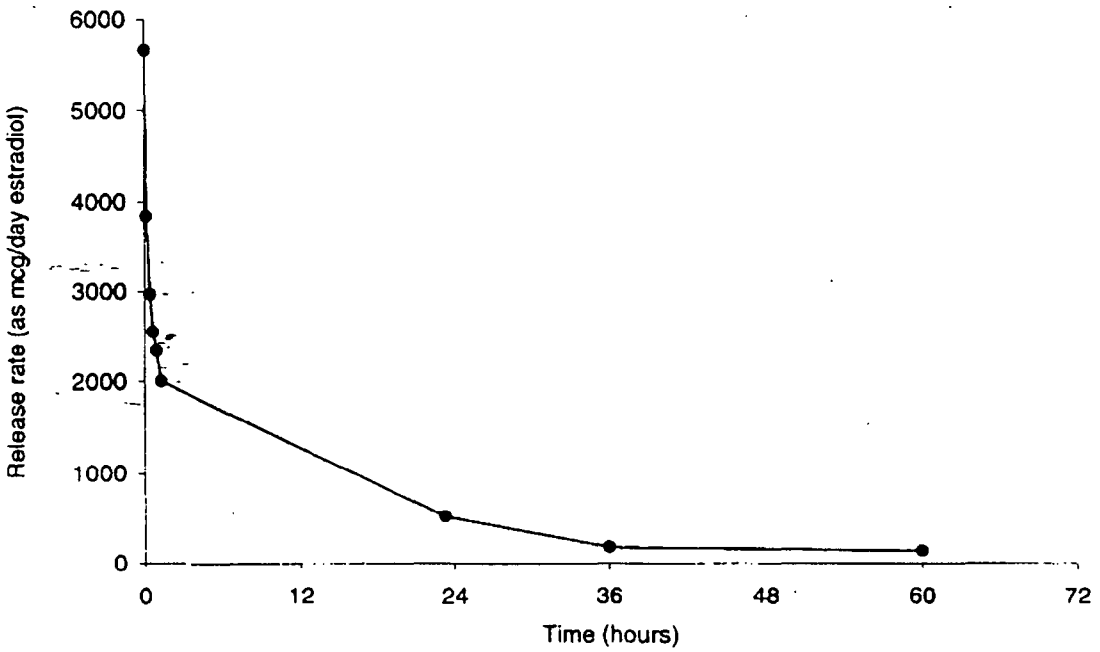


Figure 12: Mean *In Vitro* Estradiol Release Rate Profile For Rings Use in Study IVR 1005 (Lot# 960902)



What Additional Studies Were Conducted to Support the Clinical Pharmacology and PK Sections of the Labeling?

Study HRT 6A (RR 0601):

This is a dose-escalating study in healthy postmenopausal women. Each subject received three consecutive single-doses of estradiol acetate intravaginally. The rings used were 0.05 mg/day and — mg/day and were administered for two weeks each. However, 0.1 mg/day ring was administered for 12 weeks. The ages of the rings are shown in **Table 5**. There was a washout period of one-week between each treatment period. Serial blood samples were collected at appropriate intervals over 14 days and 84 days for respective treatment. **Table 13** shows the disposition of subjects relative to treatments:

Table 13: Disposition of Study Subjects (study HRT 6A):

Dose (as estradiol)	Enrolled	Completed	Evaulated
0.05 mg/day	12	12	12
— mg/day	12	12	12
0.1 mg/day (2 weeks)	12	12	12
0.1 mg/day (12 weeks)	12	11	11

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Results:

The serum concentration-time profiles show estradiol and estrone concentrations were relatively constant over 2 weeks and 12 weeks treatment periods (**Figures 13 and 14**). The serum estone profiles were parallel but slightly lower than estradiol (**Figures 15 and 16**). The mean estradiol/estrone AUC ratios for 0.05, ⁓ and 0.1 mg/day over 14 days treatments were 1.14, 1.31 and 1.48, respectively and 1.71 for the 0.1 mg/day formulation over 84-day treatment period.

It appears that there was a trend for a dose proportionality for estradiol, when considering AUC data only. However, this does not appear to apply to Cmax. Although, the Cmax and the average serum concentration of estradiol appear to increase with dose, the increase was slightly less than proportional. This observation could be due to variability in the data (**Table 14**). However, for estrone, there was less than proportional increase in both Cmax and AUC with dose (**Table 14 and Figures 15 and 16**).

Figure 13. Mean serum estradiol concentrations-time profile over 14 days following administration of estradiol acetate IVRs in 12 postmenopausal women (study # HRT 6A).

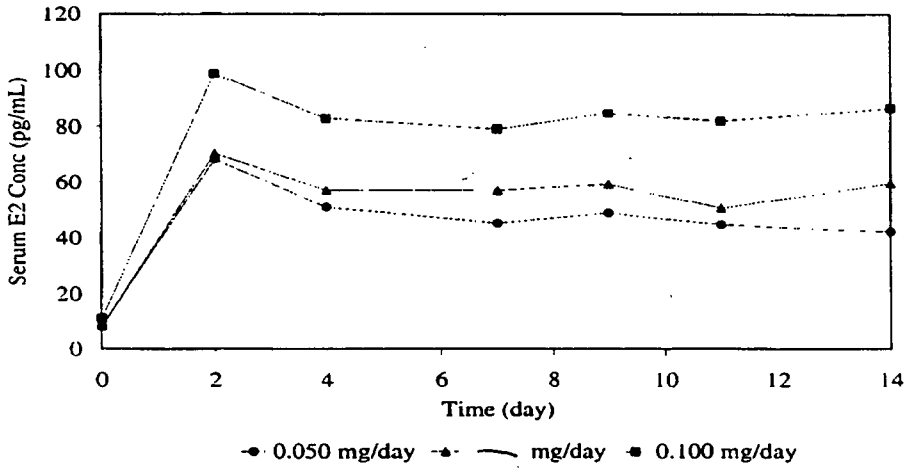

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Figure 14. Mean serum estradiol concentrations-time profile over 84 days weeks following administration of estradiol acetate IVRs 0.1 mg/day in 11 postmenopausal women (study # HRT 6A).

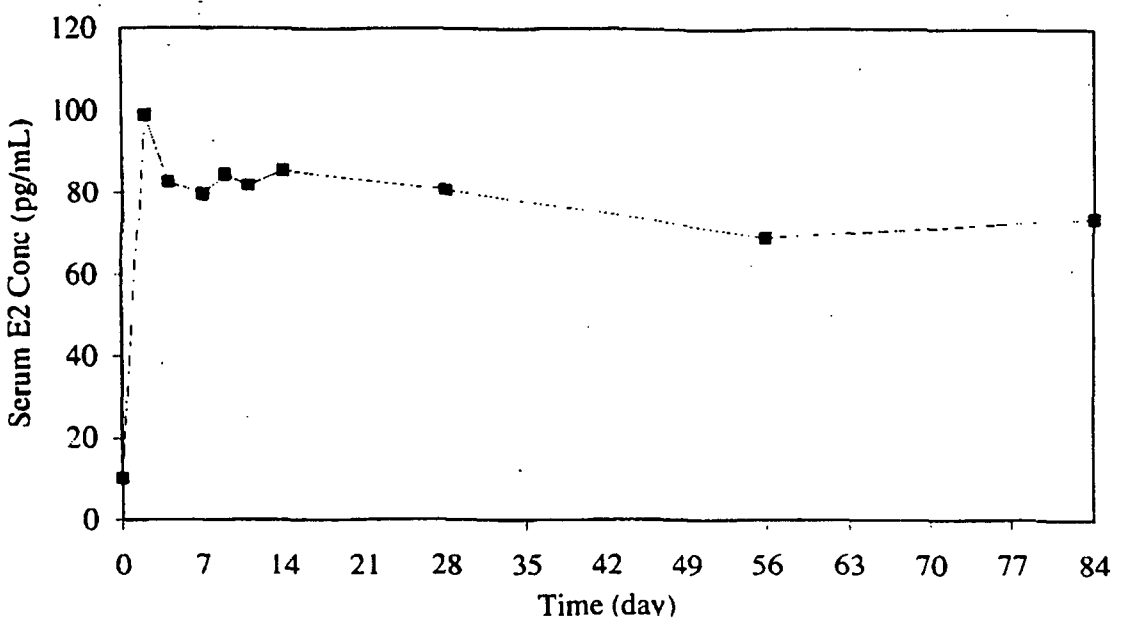


Figure 15. Mean serum estrone concentrations-time profile over 14 days following administration of estradiol acetate IVRs in 12 postmenopausal women (study # HRT 6A).

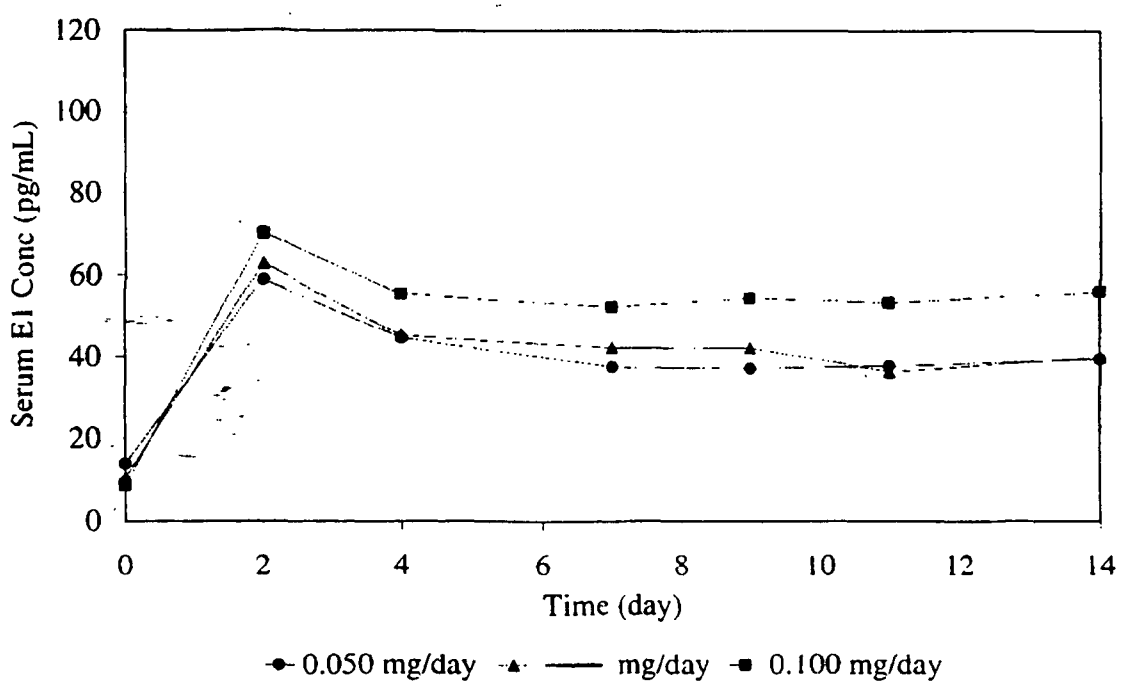


Figure 16. Mean serum estrone concentrations-time profile over 84 days weeks following administration of estradiol acetate IVRs 0.1 mg/day in 11 postmenopausal women (study # HRT 6A).

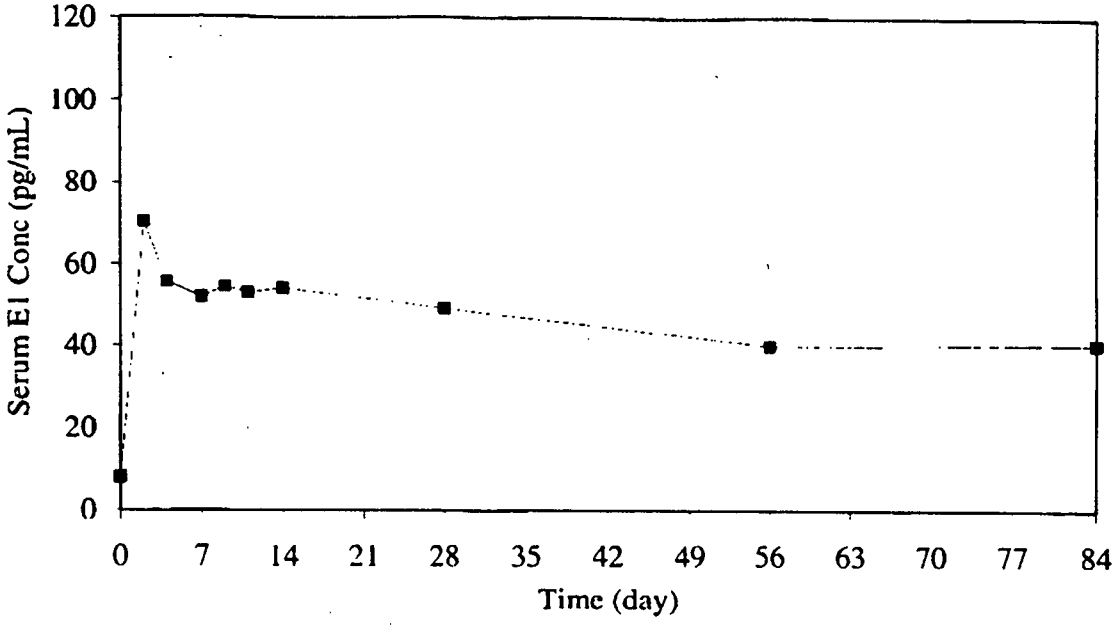


Table 14. Summary of Estradiol and Estrone PK Parameters (study # HRT 6A)

Dose (E2/day)	Analyte	n	Treatment duration (days)	Mean (%RSD)					
				Cmax[a] (pg/mL)	tmax[a] (day)	Cmin (pg/mL)	AUC(0-t) (pg·day/mL)	Cavg (pg/mL)	Percentage Fluctuation[a]
0.050	Estradiol	12	14	68.9 (37)	2.8 (93)	38.2 (58)	658 (52)	47.0	89.0 (88)
—		12	14	73.4 (34)	5.8 (79)	42.8 (35)	768 (34)	54.9	54.8 (48)
0.100		12	14	102.6 (37)	4.3 (107)	69.9 (36)	1117 (37)	79.8	41.5 (34)
0.100		11	84	105.1 (36)	18.0 (154)	62.0 (31)	6384 (24)	76.0	54.9 (33)
0.050	Estrone	12	14	60.8 (27)	3.6 (100)	30.3 (35)	566 (27)	40.4	78.2 (47)
—		12	14	63.5 (28)	2.8 (93)	32.0 (36)	590 (28)	42.2	77.0 (39)
0.100		12	14	74.5 (24)	4.2 (98)	44.0 (36)	745 (29)	53.2	61.0 (40)
0.100		11	84	75.2 (24)	5.6 (141)	35.0 (26)	3837 (25)	45.7	91.5 (37)

Conclusions:

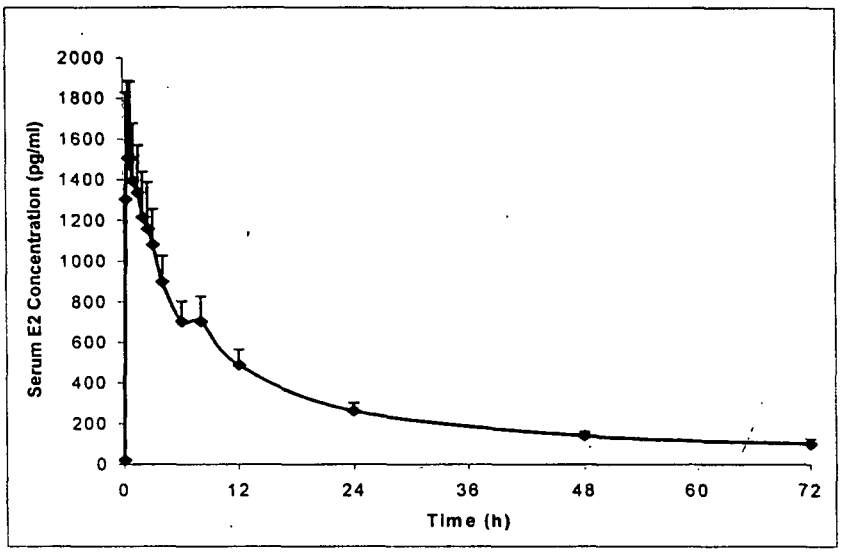
From this study it can be concluded that estradiol serum level remains relatively constant over 3 months period. The average serum estradiol concentration was 76 pg/ml following 0.1 mg/day ring.

Study IVR 1001 (RR 0071):

This is a single dose study conducted in 12 healthy postmenopausal women. Each subject received one estradiol acetate IVR 0.1 mg/day ring for 72 hours.

Within one hour, the serum estradiol concentration was rapidly and immediately declined to approximately 400 pg/ml within the first 12 hours (**Figure 17**). In this study serum estrone concentration was not determined.

Figure 17. Mean (+/-SD) Serum Estradiol (E2) Concentration-Time Profile Following Insertion 0.1 mg/day Vaginal Rings in 12 Postmenopausal Women (Study # IVR 1001)



Conclusion:

Following IVR administration, serum estradiol concentrations increased rapidly with a mean Cmax of 1665 pg/ml occurring within the first hour after administration.

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Study IVR 1006 (RR 00901):

This is a multiple-dose PK study conducted in 25 healthy postmenopausal women. Each subject received one estradiol acetate IVR 0.05 mg/day ring for 13 weeks (Dose 1, Period 1). A second dose was then administered for 4 weeks (Dose 2, Period 2) with no washout period between treatments. Serial blood samples were collected from each subject throughout each treatment period.

The primary objectives of this study were to characterize the PK profiles of the IVR in terms of estrdiol, estrone, and estrone sulfate concentrations under the following conditions:

a) At steady state over 13-week treatment period.
b) During an acute sampling period (up to three days post-insertion).
c) Following insertion of a second ring over a four-week treatment period.

Results:

The data from this study are summarized in **Figures 18-23** and **Table 15**. Again, serum estradiol concentrations increased rapidly with Cmax occurring approximately 1 hour after administration. This surge in estradiol serum concentration follows a rapid decline and then remains relatively constant over a period of 3 months after Dose 1 (**Figures 18-20**). The average serum estradiol concentration was approximately 35-40 pg/ml following administration of the 0.05 mg/day IVR for 3 months (**Table 15**)

The initial surge of estradiol serum concentration (Cmax) from Dose 2 was approximately 30% lower than that from Dose 1. However, by 2 hours there were no meaningful differences between the two profiles and were superimposable for Dose 2 and Dose 1. No differences in AUC were noted between Dose 1 and Dose 2 nor with Tmax (**Table 15**).

Estrone and estrone sulfate levels were similar following both doses (**Figures 21-23 and Table 15**). The metabolite ratios based on $AUCs_{(0\text{-}91\ days)}$ were 1.15 for estradiol:estrone and 0.10 for estradiol:estrone sulfate (**Table 15**).

Figure 18. Mean serum estradiol concentrations-time profile for Dose 1 (closed circle) and Dose 2 (open circle) from time 24 hours through 13 weeks (main plot) and from time 0 through 13 weeks (insert) following administration of 0.05 mg/day estradiol ring in 25 postmenopausal women (study # IVR 1006).

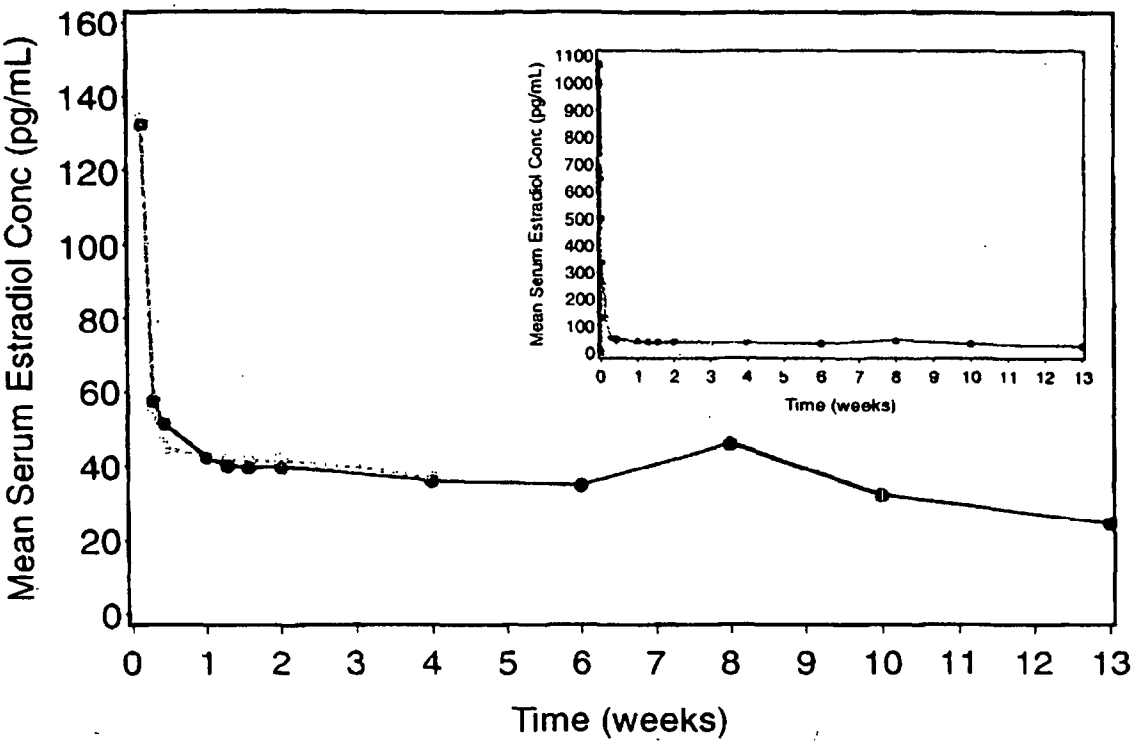

Figure 19. Mean serum estradiol and estrone concentrations-time profile for Dose 1 and Dose 2 following administration of 0.05 mg/day estradiol ring in 25 postmenopausal women (study # IVR 1006).

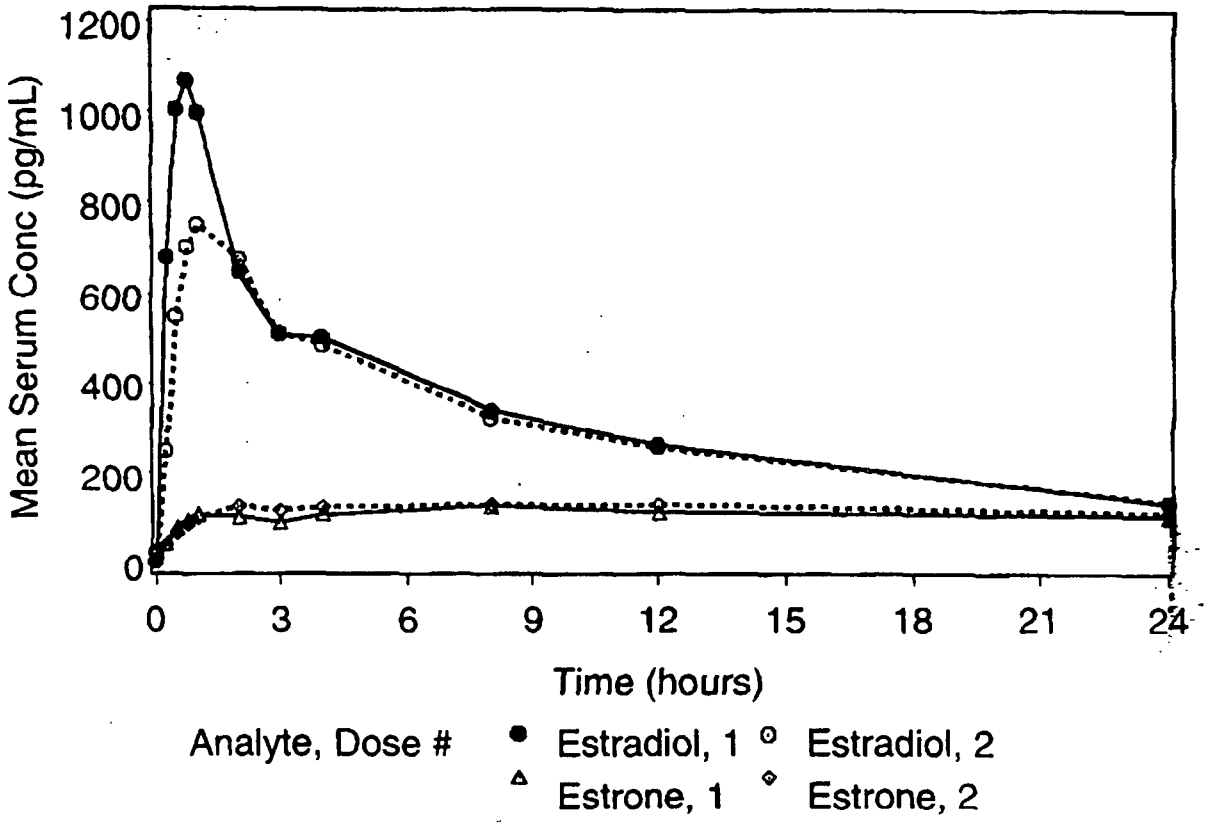

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Figure 20. Mean serum estradiol concentrations-time profile throughout the study for Dose 1 and Dose 2 of 0.05 mg/day estradiol ring in 25 postmenopausal women (study# IVR 1006).

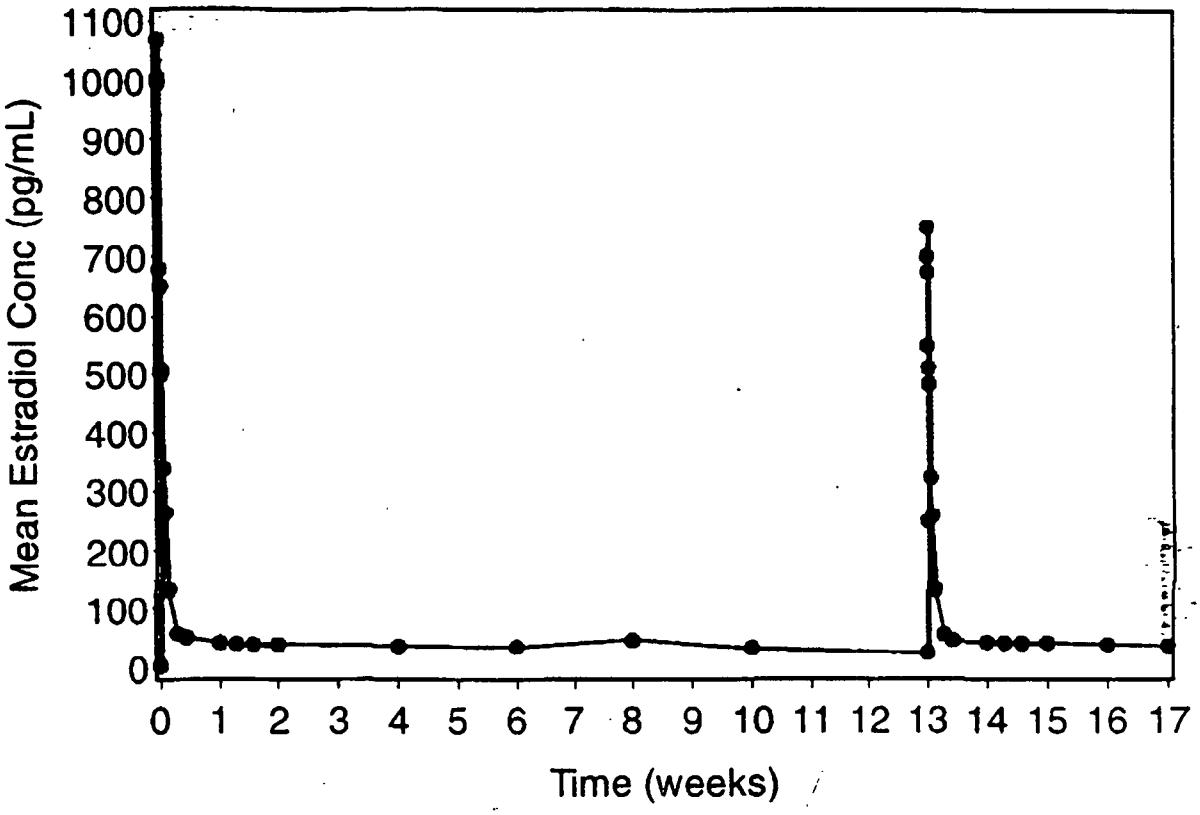

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Figure 21. Mean serum estrone concentrations-time profile throughout the study for Dose 1 and Dose 2 of 0.05 mg/day estradiol ring in 25 postmenopausal women (study #IVR 1006).

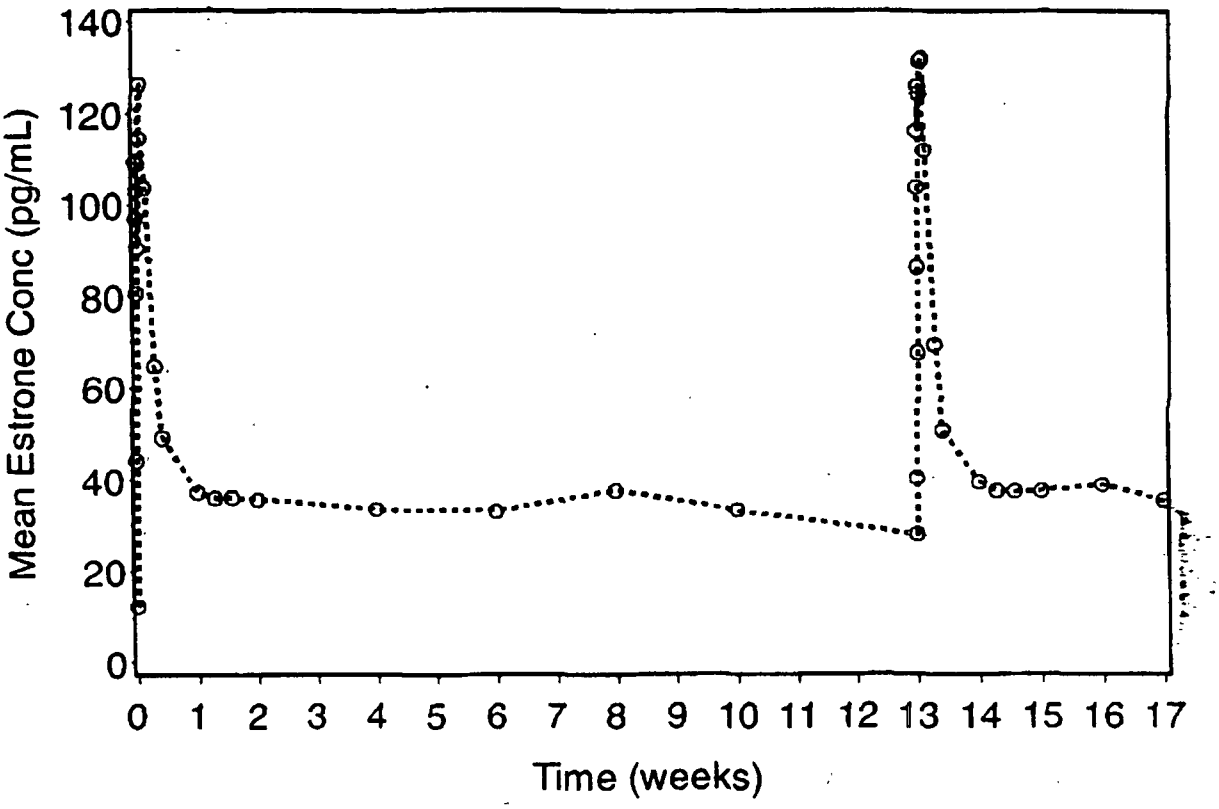

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Figure 22. Mean serum estrone sulfate concentrations-time profile for Dose 1 (open square) and Dose 2 (open circle) from time 0 to 4 weeks following administration of 0.05 mg/day estradiol ring in 25 postmenopausal women (study # IVR 1006).

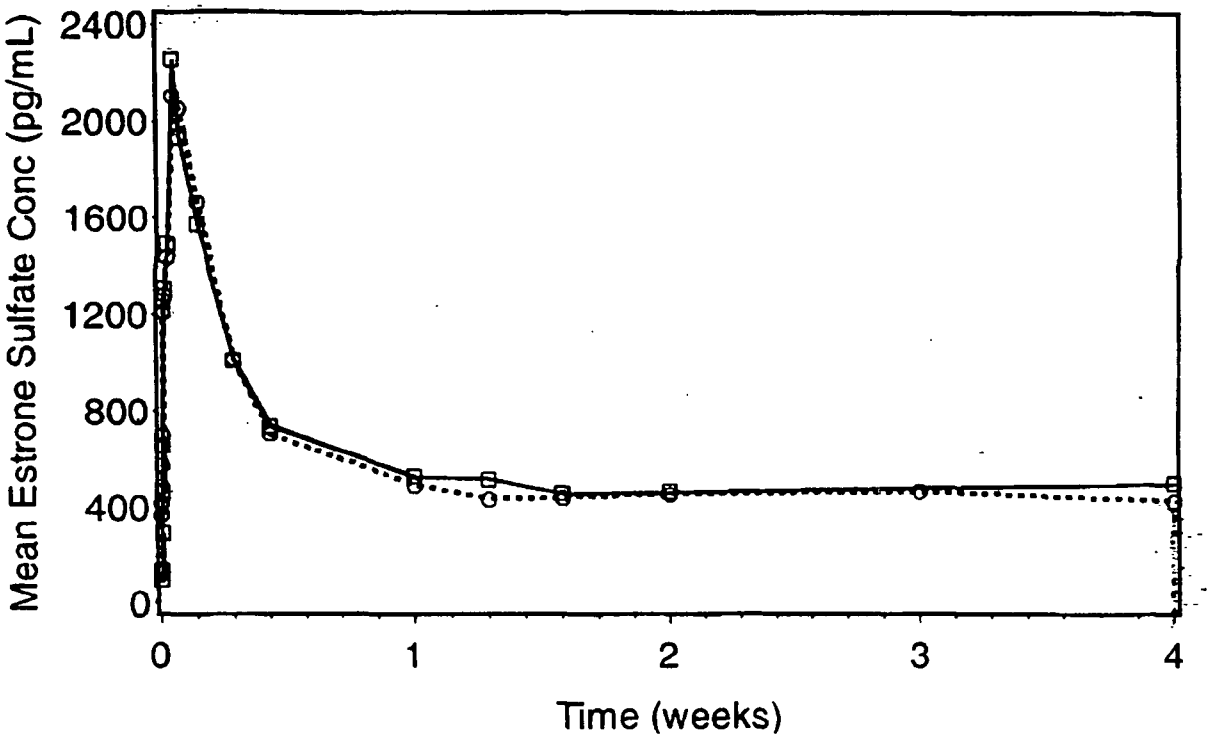

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Figure 23. Mean serum estrone sulfate concentrations-time profile for Dose 1 (day 0) and Dose 2 (Day 13) of 0.05 mg/day estradiol ring in 25 postmenopausal women (study # IVR 1006).

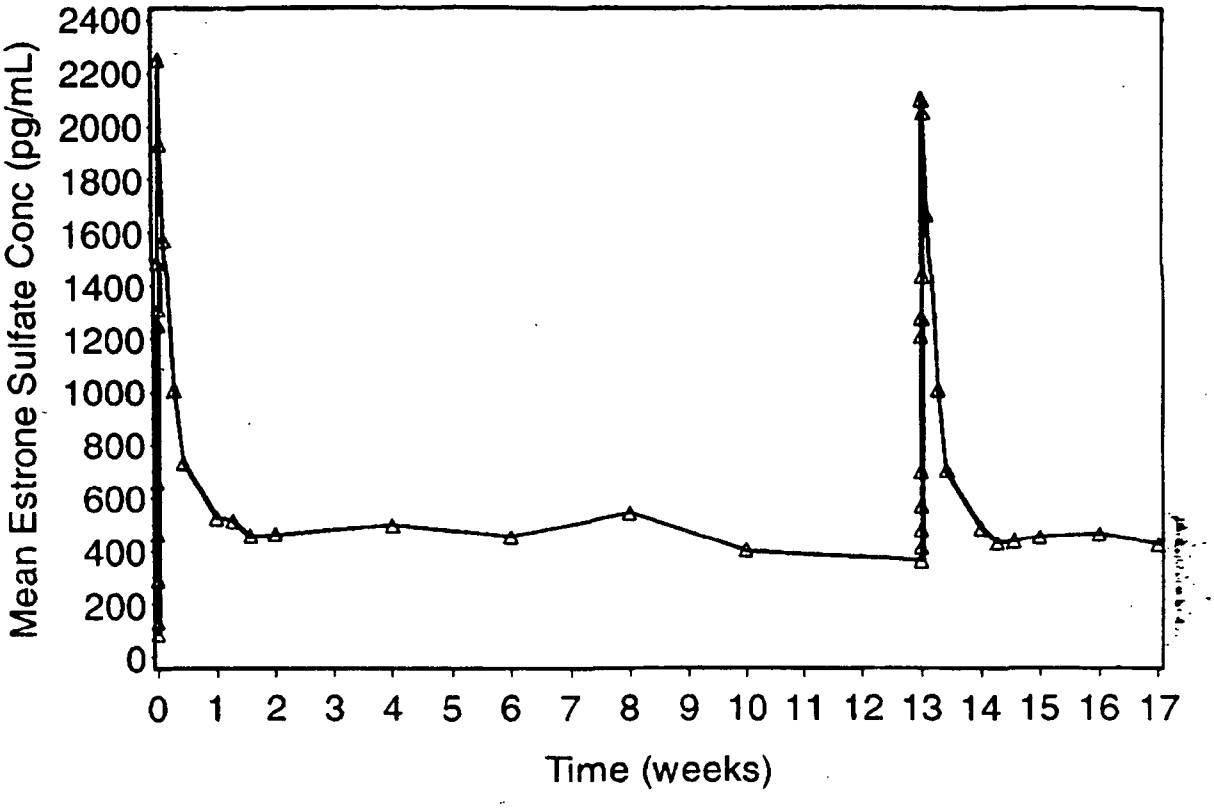

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Table 15. Summary of estradiol, estrone, and estrone sulfate PK parmaters values following administration of Dose 1 and Dose 2 of 0.05 mg/day estradiol ring to 25 postmenopausal women (study # IVR 1006).
Keys: E1 = estrone, E2 = estradiol, E1-S = estrone sulfate

		Dose 1 Mean (%RSD)	Dose 2 Mean (%RSD)	% Difference[a]	95% Confidenc Interval[a]
Estradiol	Cmax (pg/mL)	1129 (25)	772 (25)	-31.3	-38.2 to -23.8
	tmax (h)	0.9 (41)	1.1 (40)	21.6	-6.6 to 49.8
	AUC(0–91) (pg*day/mL)	3695.9 (26)	--	--	--
	Cavg(0–91) (pg/mL)	40.6 (26)	--	--	--
	AUC(0–28) (pg*day/mL)	1485.0 (29)	1473.8 (21)	0.3	-5.5 to 6.4
	Cavg(0–28) (pg/mL)	53.0 (29)	52.6 (21)	--	--
	Cmin (pg/mL)	22.8 (23)	34.0 (26)	--	--
	Fluctuation (%)	2815.1 (24)	1431.6 (25)	--	--
Estrone	Cmax (pg/mL)	141 (25)	149 (25)	5.5	-4.5 to 16.6
	tmax (h)	6.2 (84)	8.8 (69)	41.9	-7.0 to 90.9
	AUC(0–91) (pg*day/mL)	3270.3 (21)	--	--	--
	Cavg(0–91) (pg/mL)	35.9 (21)	--	--	--
	AUC(0–28) (pg*day/mL)	1163.8 (25)	1249.3 (18)	8.4	1.8 to 15.4
	Cavg(0–28) (pg/mL)	41.6 (25)	44.6 (18)	--	--
	Cmin (pg/mL)	25.8 (23)	32.3 (21)	--	--
	Fluctuation (%)	324.8 (24)	262.4 (24)	--	--
Estrone Sulfate	Cmax (pg/mL)	2365 (44)	2292 (41)	-2.2	-11.7 to 8.4
	tmax (h)	9.3 (39)	9.9 (47)	6.9	-17.6 to 31.4
	AUC(0–91) (pg*day/mL)	45006.8 (48)	--	--	--
	Cavg(0–91) (pg/mL)	494.6 (48)	--	--	--
	AUC(0–28) (pg*day/mL)	16641.8 (52)	15729.0 (41)	-3.2	-11.3 to 5.7
	Cavg(0–28) (pg/mL)	601.3 (54)	561.8 (41)	--	--
	Cmin (pg/mL)	137.4 (46)	344.4 (39)	--	--
	Fluctuation (%)	472.3 (28)	359.2 (26)	--	--
Metabolite Ratios	E2:E1(0–91)	1.15 (23)	--	--	--
	E2:E1-S(0–91)	0.10 (52)	--	--	--
	E2:E1(0–28)	1.29 (22)	1.20 (23)	-7.5	-13.5 to -1.5
	E2:E1-S(0–28)	0.11 (53)	0.11 (70)	4.7	-11.3 to 20.8

Conclusions:

There was no PK or clinically meaningful differences between Dose 1 and Dose 2. The surge in estradiol serum concentration was always noted in all cases and occurring immediately after the ring insertion. This surge was immediately followed by a rapid decline in serum estradiol concentration and reaching a plateau level after one week.

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Study IVR 1002 (RR 01101):

This is the pivotal Phase III trial. It is a double-blind, placebo controlled, parallel group, in postmenopausal women experiencing moderate to severe hot flushes. Serial blood samples were collected at screening, at dosing, and at 4, 8, and 13 weeks of treatment period for the determination of serum estradiol and estrone concentrations. Patients received one of the following treatments: placebo, 0.05 or 0.1 mg/day rings. The total number of patients entered the study was 108, 113, and 112 and those completed the entire study up to 13 weeks was 70, 89, 87 for placebo, 0.05, and 0.1 mg/day groups, respectively.

Results:

In this study no early blood samples were collected to determine the initial surge in estradiol serum level. The first blood sample collected in this study was 4 weeks after the ring insertion when estradiol serum level was at the plateau phase. Nevertheless, based on this study, estradiol serum concentration-time profile remains relatively constant throughout the dosing intervals (**Figure 24**). At this point, there was no apparent dose proportionality in serum estradiol level following 0.05 and 0.1 mg/day doses (**Figure 24 and Tables 16-17**). The overall average serum estradiol level for week 4, 8, and 13 was approximately 40 and 65 pg/ml following 0.05 and 0.1 mg/day dose, respectively (**Tables 16-17**). For estrone, however, there was clear less than proportional increase in its serum level as the dose increased from 0.05 mg/day to 0.1 mg/day (**Figure 25 and Tables 16-17**). It should be noted that the baseline of estradiol concentration was rather high compared to the values at screening in the cohort assigned to receive the 0.05 and 0.1 mg/day doses. The reason for this is not clear, but could be due to variability in the data.

Conclusions:

Estradiol and estrone serum levels remain relatively constant over the entire study period. It appears that there is less than proportional increase in estradiol and estrone level as the dose increased from 0.05 to 0.1 mg/day. This observation is more clearly define for estrone serum level than estradiol.

Figure 24. Mean serum estradiol concentrations-time profile (study # IVR 1002).

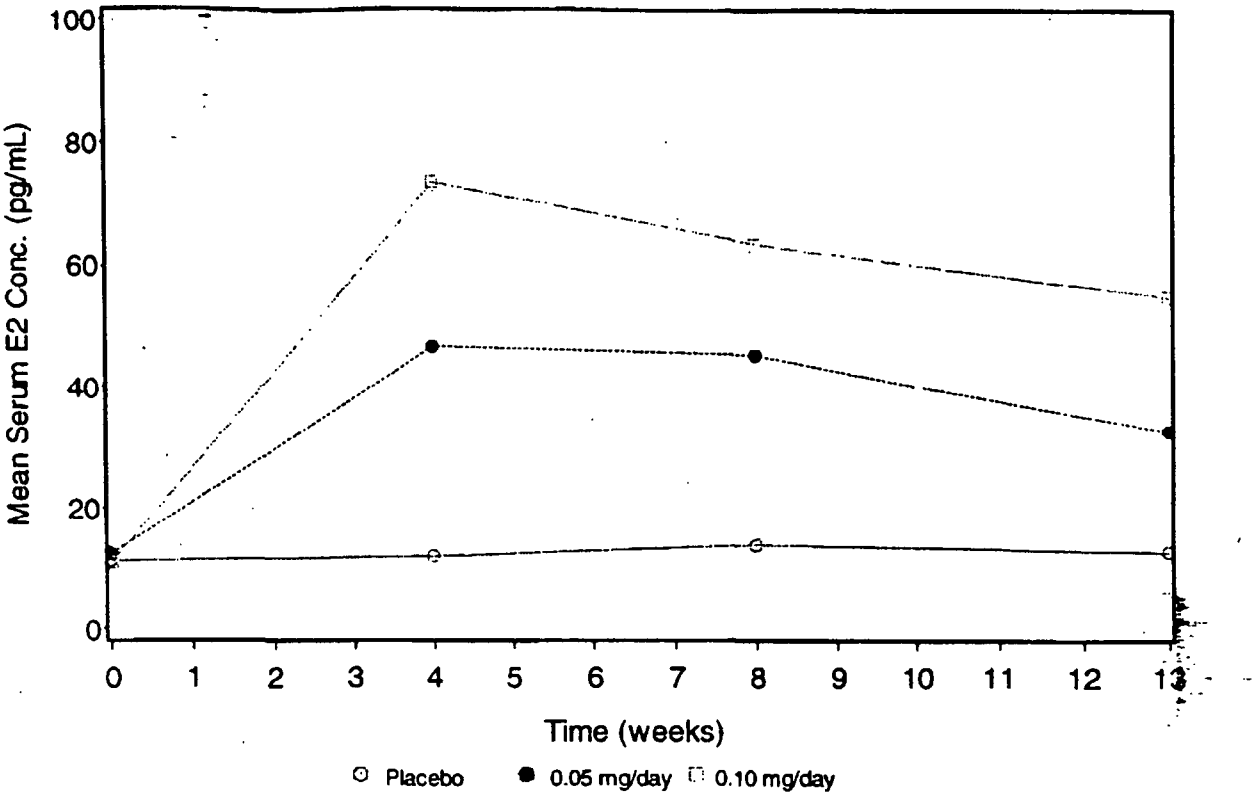

Figure 25. Mean serum estrone concentrations-time profile (study # IVR 1002).

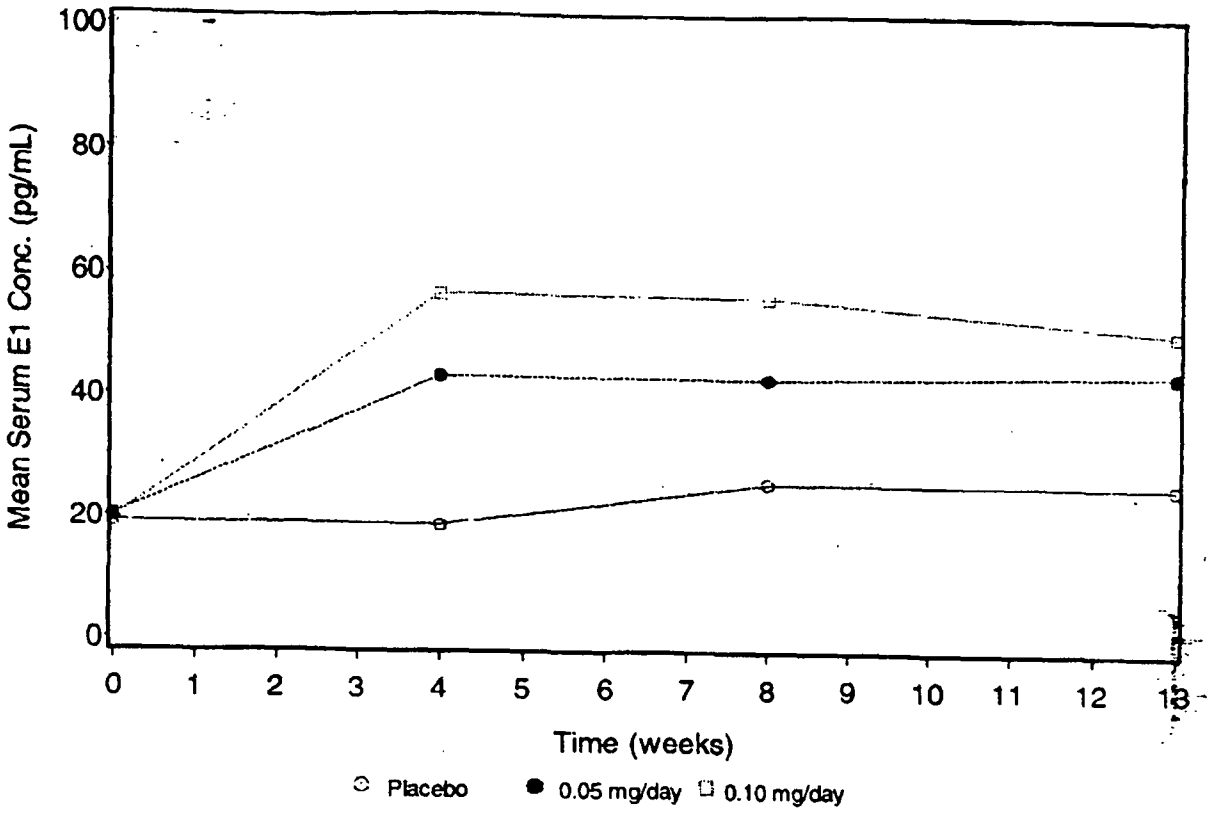

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Table 16. Summary of estradiol and estrone serum concentrations (study # IVR 1002).

	Mean (%RSD, n) Serum Estradiol Concentration (pg/mL) by Sample Time				
	Screening	Baseline	Week 4	Week 8	Week 13
Placebo	11.2 (102, 108)	11.8 (120, 104)	12.0 (158, 90)	13.9 (158, 74)	12.8 (320, 70)
0.05 mg/day	12.4 (115, 113)	60.9 (273, 109)	46.6 (84, 94)	45.1 (109, 94)	32.6 (90, 89)
0.10 mg/day	11.0 (106, 112)	56.8 (225, 109)	73.5 (48, 102)	63.4 (54, 92)	54.9 (62, 87)
	Mean (%RSD, n) Serum Estrone Concentration (pg/mL) by Sample Time				
	Screening	Baseline	Week 4	Week 8	Week 13
Placebo	18.9 (126, 108)	19.2 (100, 103)	18.6 (117, 90)	25.6 (83, 74)	25.2 (181, 70)
0.05 mg/day	20.1 (80, 113)	22.8 (84, 109)	43.3 (46, 94)	42.8 (53, 94)	43.8 (126, 89)
0.10 mg/day	19.7 (74, 112)	24.8 (187, 109)	56.6 (50, 102)	56.0 (58, 92)	50.6 (44, 87)
Cavg = Mean of Week 4, 8 and 13 serum concentration values.					

Table 17. Overall (compiled) summary of estradiol and estrone serum concentrations for week 4, 8, and 13 (study # IVR 1002).

Estradiol	Mean (%RSD, n)			Difference	95% Confidence Interval
	Screening	Cavg (4, 8, 13 weeks)	Baseline Adjusted Cavg		
Placebo	11.2 (102, 108)	12.8 (219, 234)	NS	-	-
0.05 mg/day	12.4 (115, 113)	41.6 (90, 277)	29.1 (129, 277)	96%	71.8 to 124.4
0.10 mg/day	11.0 (106, 112)	64.4 (92, 281)	54.2 (66, 281)		

NS – no significant difference between Cavg and screening estradiol concentration.

Difference – Difference between log-transformed baseline-adjusted Cavg values for 0.05 and 0.10 mg/day IVR, expressed as a percentage of 0.05 mg/day value

95% Confidence Interval – 95% confidence interval for difference between log-transformed baseline-adjusted Cavg values for 0.05 and 0.10 mg/day IVR, expressed as a percentage of 0.05 mg/day value

Was There Any Safety Concerns or PK/PD Relationship During Clinical Trials?

This is a brief summary of the clinical pharmacology related information from the two clinical trails submitted in this NDA. It should be emphasized that this summary of the clinical pharmacology related data should never be considered as a summary of the clinical trails to determine the safety and efficacy of the rings. Therefore, for more details on the safety and efficacy of ———, please refer to the Medical Officer's reviews and comments. Two main clinical studies were conducted to determine the safety and efficacy of the ———study # HRT 8 and IVR 1002. The primary efficacy parameter in both studies is the relief from hot flushes (HS), night sweats (NS), and corresponding ratio (HF/NS). These observations were recorded daily using diary cards. Other efficacy/safety parameters were also assessed such as lipid profiles, bone mineral density, endometerial biopsies and bleeding patterns.

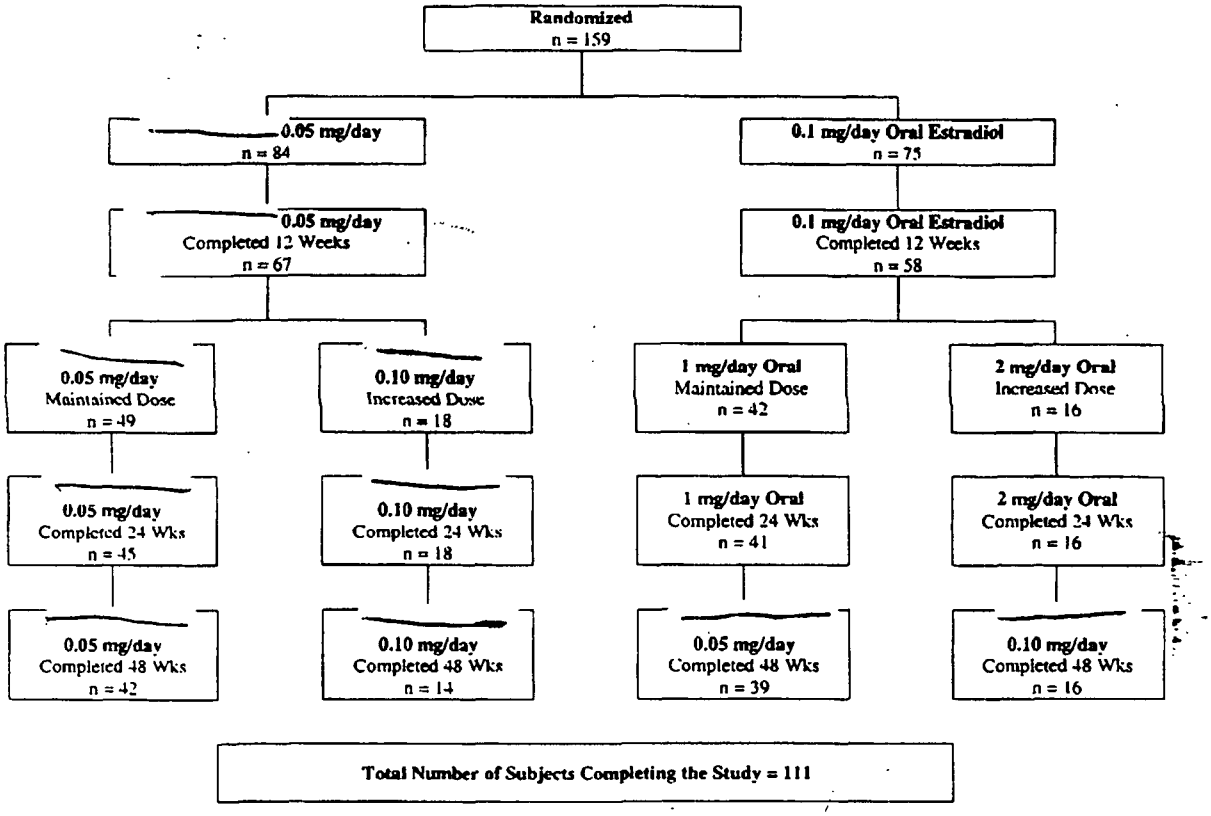
Study # HRT 8:

Briefly, this was a supportive comparative trail in 50 subjects following oral and vaginal administration for 6 months. It was designed as a double blind, multicenter, randomized, comparator-controlled, parallel group study in healthy postmenopausal women. Subjects received either ———0.05 mg/day ring or 1 mg/day oral estradiol for 24 weeks. After 12 weeks of treatments those subjects on active treatments were switched to their respective treatments of either 0.1 mg/day ring or 2 mg/day oral estradiol for further 24 weeks (**Table 18**). In all cases, there were approximately 50 women in each group. The main objectives of this study were as follows:

1) To compare the efficacy of oral estradiol to ———
2) To investigate the effect of two treatments on ———
3) To asses the effect of both treatments on ———
4) To establish the safety and acceptability of ——— relative to daily oral estradiol administration.
5) To evaluate the systemic and local vaginal tolerability.

A total of 159 subjects were randomized in the study. A total of 111 completed the 48 weeks of the study as follows: 42 and 14 subjects on 0.05 and 0.1 mg/day of ——— .treatment and 39 and 16 subjects in the 1 and 2 mg/day oral estradiol, respectively. The latter groups were switched to 0.05 and 0.1 mg/day — According to the sponsor memo dated September 12, 2002 and the fax dated August 30, 2002, a total of 30 subjects (16 + 14) were exposed to the 36 months old 0.1 mg/day rings (see also **Table 5 and Table 18**). No PK data were collected in this study. For clarification on the subject's disposition and randomization, please refer to the flow chart (**Table 18**).

Table 19. Subjects Disposition Flow Chart at Each Arm of Study HRT 8.



The primary efficacy measure in this study was the ratio of Hot Flushes (HF)/Night Sweats (NS). In this study no PK data were collected. **Figure 26** shows the number of HF/NS at each week of treatment. The oral administration appears to be slightly better than that of the intravaginal. The frequencies of HF/NS in both groups plateau within the first 5-6 weeks of treatments. The percent reduction in the number of HF/NF from baseline was 84.1% and 72.8% at 12 weeks and 94.1% and 83.2% at 24 weeks in the IVR and oral groups, respectively. The difference between the two treatments does not appear to be clinically significant. The IVR route provides a better advantage over PO administration in terms of convenience and less fluctuation in estradiol serum levels. In contrast to PO route, IVR does not require daily administration and is not associated with daily peaks in serum estradiol levels. Based on this study, the safety profiles of PO and IVR routes appear to be comparable.

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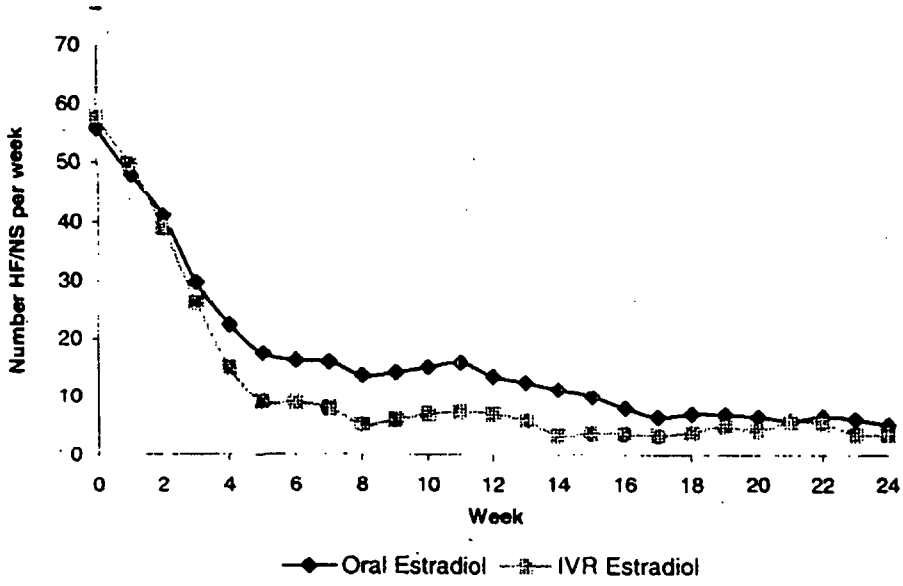
Figure 26. Number of Hot Flushes (HF)/Night Sweats (NS) at each Treatment (Study # HRT 8)



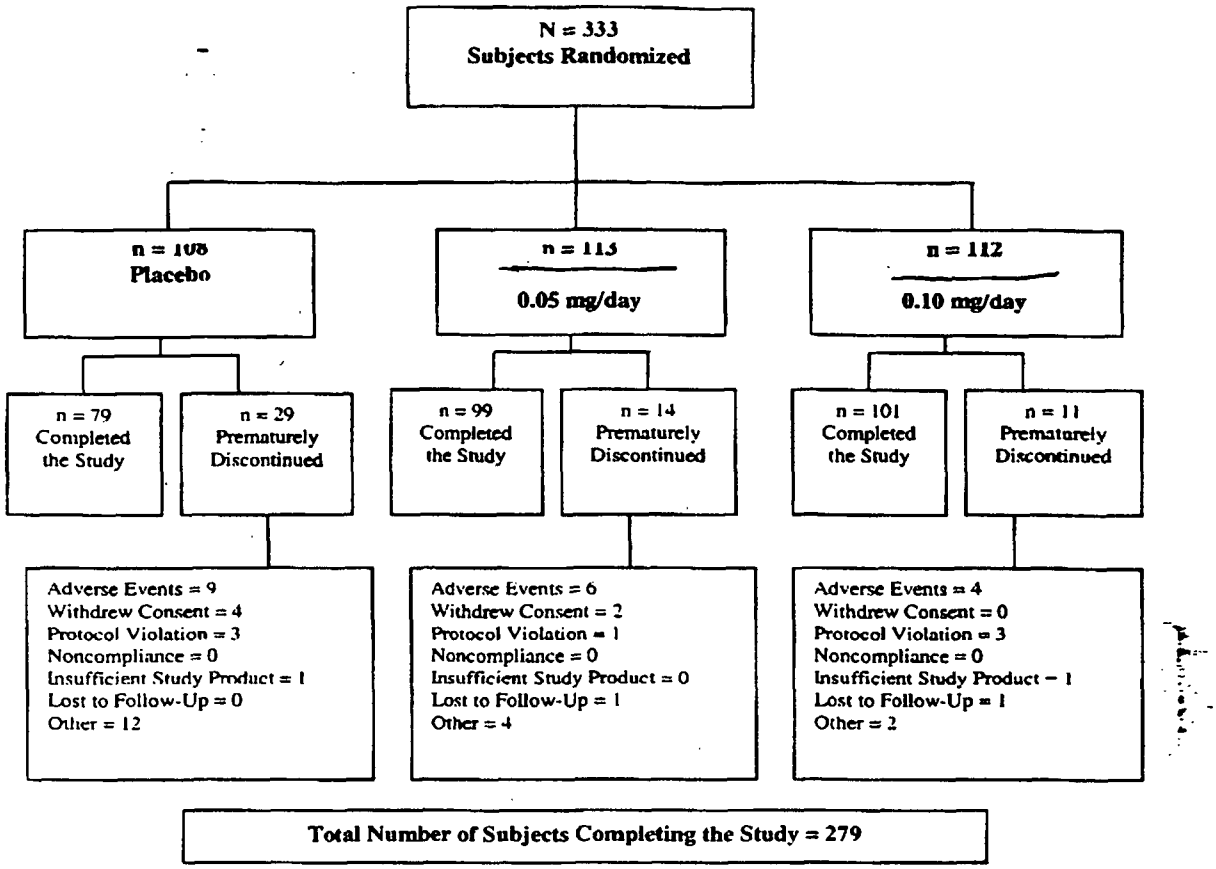
IVR 1002:

As described above, IVR 1002 was the pivotal Phase III study. The clinical objectives of this study were as follows:

1) To determine the efficacy in terms of relief of hot flushes.
2) To assess vaginal atrophy.
3) To establish safety and acceptability.
4) To determine systemic and local vaginal tolerability.

There were 333 subjects enrolled in this study randomized into three groups: Group A (placebo, n=108), Group B (———— 0.05 mg/day, n=113) and Group C (———— 0.1 mg/day, n=112). The total number of subjects completed the study was 279 as follows: Group A (n=79), Group B (n=99) and Group C (n=101). Therefore, the total number of subjects discontinued the study for various reasons was 54 (15.2%). No PK data were collected in this study. **Table 19** show the disposition of the subjects and the number of drop out at each arm of the study.

Table 19. Subjects Disposition Flow Chart at Each Arm of Study IVR 1002.



As shown in **Figures 27,** the mean changes from baseline in moderate to severe vasomotor symptoms (MSVS) on ——— were significantly greater than the placebo group at weeks 2 through week 13 ($p<0.05$). **Figure 28** shows the mean change from baseline for vaginal atrophy. Both doses demonstrated superiority to placebo ($p<0.05$). However, it does not appear there was much difference in response between the two does of 0.05 and 0.1 mg/day. Therefore, the clinical significance of the difference between the two doses remains to be established (please see the medical officer review).

Figure 27. Mean Change From Baseline in the Number of MSVS (Moderate Severe Vasomotor Symptoms) at each Week (Study # IVR 1002)

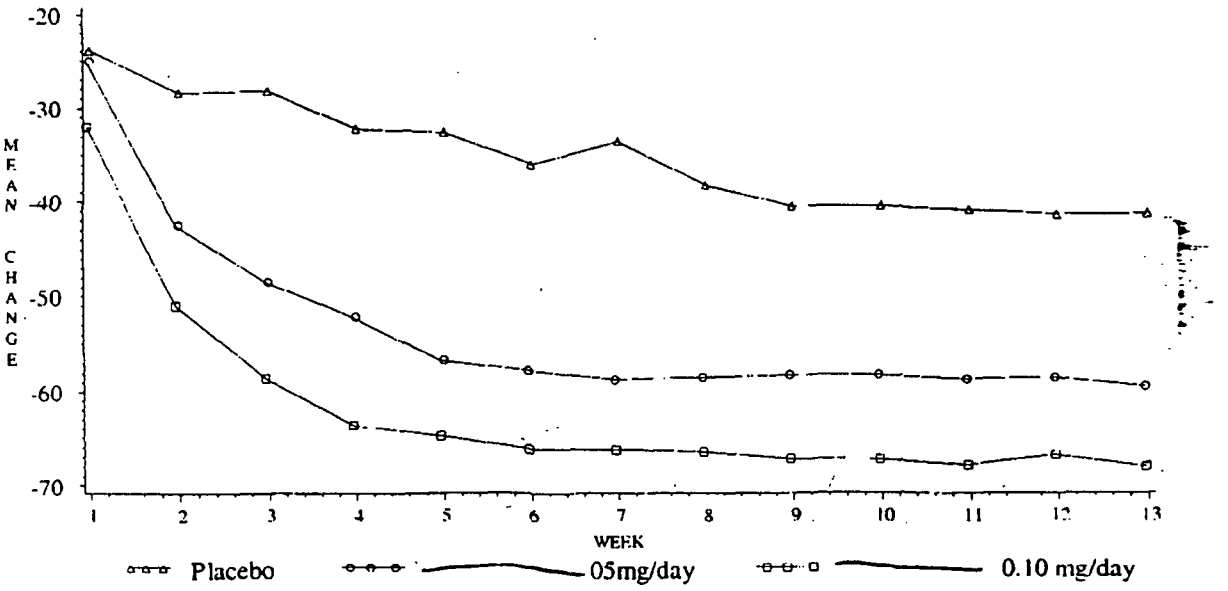


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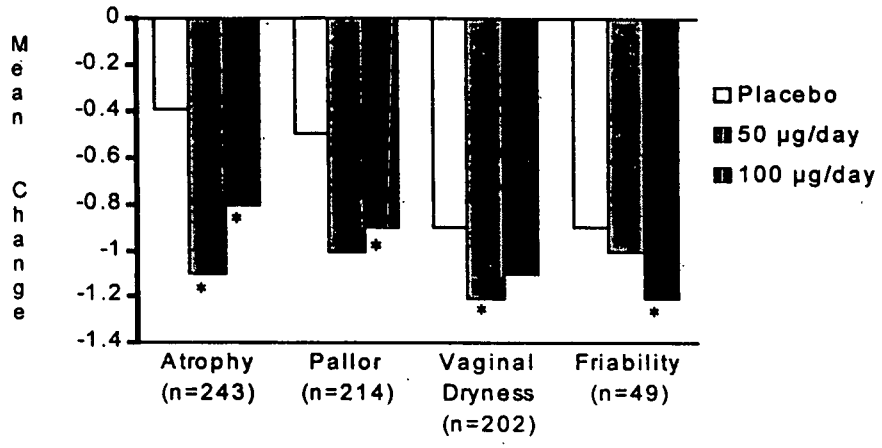
Figure 28. Mean Change From Baseline in severity of Findings of Vaginal Atrophy (study IVR 1002). * p<0.05 versus placebo



Conclusions:

From Phase III studies, the following conclusions can be made:

1) Both strengths show clinically significant efficacy compared to placebo.
2) There was a clear dose-response relationship in terms of the efficacy. The 0.1 mg/day was slightly superior to 0.05 mg/day rings.
3) There were no obvious clinically related adverse events relative to the age of the ring. This is in reference to the 30 subjects who were exposed to the 36 months old 0.1/day rings.

For further details and conclusions, please see the medical officer's review.

ClinPharm/Biopharm Briefing on: October 7, 2002 (2:00-3:30 PM)

Briefing Attendees: Drs.

Reviewed by:

Sayed Al Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____

cc: NDAs # 21-319: HFD-580, HFD-860 (Al-Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

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

/s/

Ameeta Parekh
10/18/02 01:18:06 PM
BIOPHARMACEUTICS

A cover memo addressing the pending issues has been attached to the incomplete review by Dr. Sayed Al Habet. Dr. Al Habet had an emergency and could not complete the review by the action date. This memo was discussed with John Hunt.

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