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APPLICATION NUMBER:

20-874

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 20-874
Lunelle™ Monthly Contraceptive Injection (medroxyprogesterone acetate and estradiol cypionate)
Pharmacia & Upjohn

Biopharmaceutics Review

No review necessary for this review cycle.

9/27/00

Jennifer Mercier, Regulatory Project Manager
HFD-580

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8:32

NDA 20-874

Lunelle™ Monthly Contraceptive Injection
(medroxyprogesterone acetate and estradiol cypionate)

Pharmacia & Upjohn
4S

PM: Jennifer Mercier

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HFD-580

Submission Date: April 7, 2000
User Fee Goal Date: October 7, 2000

Clinical Section

SEP 30 1999

Clinical Pharmacology & Biopharmaceutics Review

NDA:	20-874
Product Trade Name:	LUNELLE™ Monthly Contraceptive Injection
Active Ingredient/s:	Medroxyprogesterone Acetate and Estradiol Cypionate
Indication:	Contraception (intramuscular)
Submission Date:	April 15, 1999
Sponsor:	Pharmacia and Upjohn
Type of Submission:	Resubmission (response to "non-approval")
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

Synopsis

LUNELLE™ Contraception Injection, manufactured by Pharmacia and Upjohn Company as a sterile aqueous suspension, is a combination of medroxyprogesterone acetate (a progesterone derivative, MPA, — mg/ml) and estradiol cypionate (an estradiol ester, E_2C, — mg/ml). Each 0.5-ml injectable dose contains 25 mg MPA and 5 mg E_2C. The product is intended for deep intramuscular (IM) injection once every 28 days for the prevention of pregnancy.

Background

NDA 20874 was originally submitted (as CYCLO-PROVERA) on September 25, 1997 and was judged to be non-approvable (September 25, 1998 non-approval letter) based on inadequate information on safety and efficacy of this product. On April 15, 1999, the sponsor resubmitted the current studies and results in response to the deficiencies outlined in the non-approval letter. Angelica Dorantes, Ph.D., reviewed the Clinical Pharmacology and Biopharmaceutics section of the original submission. She concluded that if there were no other safety, the application WAS approvable with certain Phase IV commitments (PK/PD studies and assay validation results, some of which have been submitted with this resubmission).

The current resubmission has two studies with extensive PK information. The first independent study was designed to determine the PK of MPA and E_2 at steady state following 3 monthly injections of LUNELLE and also to evaluate whether a significant PK-PD relationship existed. The second study (a part of a larger clinical trial) was conducted to determine the effects of the site of injection and body mass index on the PK of MPA.

Recommendation

Based on the review, NDA 20-874 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A review of the PK data of this submission resulted in certain changes in the appropriate sections of the product label. The suggested changes are included in the section "Labeling Comments", which have already been forwarded to the Medical Officer (and subsequently to the sponsor).

/S/ Dated 9/30/99

Dhruba J. Chatterjee, Ph.D.,
Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D. /S/ Dated- 9/30/99

CC: NDA 20-874, HFD 870 (M. Chen, A. Parekh, DJ. Chatterjee), HFD-580 (D. Hixon, J. Mercier), CDR (B. Murphy for drugs).

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Background

LUNELLE™ Contraception Injection, manufactured by Pharmacia and Upjohn Company as a sterile aqueous suspension, is a combination of medroxyprogesterone acetate (a progesterone derivative, MPA, ——— and estradiol cypionate (an estradiol ester, E_2C, ———). Each 0.5-ml injectable dose contains 25 mg MPA and 5 mg E_2C. The product is intended for deep intramuscular (IM) injection once every 28 days. Pharmacologically, such combination products for oral contraception are designed so that, according to the sponsor, the progestin component (MPA) suppresses ovulation by inhibition of the gonadotropins, while the estrogenic component (E_2C) maintains a regular menstrual bleeding pattern.

NDA 20874 was originally submitted on September 25, 1997 and was judged to be non-approvable (September 25, 1998 non-approval letter) based on inadequate information on safety and efficacy of this product. On April 15, 1999, the sponsor resubmitted the current studies and results in response to the deficiencies outlined in the non-approval letter. The original submission was reviewed by Angelica Dorantes, Ph.D., of OCPB (please refer to the review dated July 1, 1998). In the review it was found that the submission relied heavily on referenced articles, the studies for which did not provide much accuracy or validation information on the analytical methods. At that time, some of the studies that have been currently submitted were ongoing, and Dr. Dorantes had concluded that a final recommendation could be made on review of those results. Based on the above findings, OCPB recommended that if there were no other safety concerns, the application WAS approvable with certain Phase IV commitments (PK/PD studies and assay validation results, some of which have been submitted with this resubmission). Few modifications on the labeling were also recommended, which primarily addresses the possible implications of higher exposure on the 'time-to-return-to-ovulation'. Since this current resubmission deals with just a study each on pharmacokinetics (PK) and pharmacodynamics (PD), please refer to the review of NDA 20-874 by Angelica Dorantes for details of the original submission (as in Appendix II).

Review of Human PK/Biopharmaceutics Studies

Study I: Protocol # M/5415/0006

Objectives:

There has not been much pharmacokinetic/pharmacodynamic information available on this product in the human population. The objectives of this study were, 1) to characterize steady-state pharmacokinetics of MPA and 17β-E_2 (17-β–estradiol) after the third monthly injection of LUNELLE, 2) to assess the return of ovarian function (i.e., return of ovulation) in surgically sterile females by measurement of serum progesterone concentrations, and 3) to determine effects of LUNELLE on serum concentrations of androgens and sex hormone-binding globulin (SHBG).

Study Design:

This was an open-label, multiple-dose study in 16 healthy (age 18 – 45 yrs), surgically sterile (via tubal ligation) females (BMI 18 – 27). The study design consisted of a pretreatment period (control cycle), a treatment period (3 x 28 days), and a follow-up period of 8 weeks (the follow-up period was later extended to 20 weeks via protocol amendment). During the control cycle, serum progesterone concentrations were measured for 26-32 days to confirm the presence of a normal menstrual cycle and ovulation. Subjects with confirmed ovulation received the study drug every 28 days for 3 consecutive injections. Immediately after the third injection and throughout the follow-up period, recurrence of ovulation was monitored as evidenced through changes in serum progesterone concentrations.

During the treatment phase of the study, each subject received the first injection (0.5 ml) of LUNELLE within the first 5 days of the onset of menstrual bleeding. The second injection was administered 28 days after the first dose. The third injection was administered 28 days after the second dose. Prior to each dose, the sterile aqueous suspension of investigational drug was vigorously shaken just before withdrawal into the syringe to ensure the dose was administered as a uniform suspension of MPA: E2C. The injections (0.5-mL dose) were given into the gluteal muscle (hip) using needle size [redacted] to ensure deep IM injection.

Each subject had blood drawn during Days 3-7 and on Days 12, 14, 18, 21, and 28 of the pretreatment control cycle. These samples were assayed for serum 17β-E_2 and progesterone to confirm the occurrence of ovulation. Serum 17β-E_2 levels ≥150 pg/ml and progesterone concentrations ≥3 ng/ml are indicative of follicular and luteal activity, respectively. In this study, ovulation was confirmed by serum progesterone concentrations ≥4.7 ng/ml [Aedo 1985]. This determination was to be made by averaging progesterone concentrations from samples collected on Days 18 and 21 of the control cycle. Subjects with progesterone levels below this threshold were not to be allowed to continue to the treatment portion of the study.

On Days 1, 29, and 57 of the treatment phase, just prior to each dose of LUNELLE, blood were collected for determination of trough levels of MPA, 17β-E_2 and for progesterone measurement. Following the third dose, blood samples were drawn on Days 58 (24 hours post-dose), 60, 62, 64, 67, 69, 71, 75, 78, 85 and weekly thereafter through Day 141 for pharmacokinetic and pharmacodynamic analyses.

Results & Conclusions:

(i) Pharmacokinetics:

Please refer to the APPENDIX I for tables and figures. Relevant pharmacokinetic parameters are summarized in Table I. Figure 1 A-B describes the mean plasma concentration time profile of MPA and E_2 following the 3rd monthly IM injection of LUNELLE.

Mean serum MPA concentrations peaked at 3.5 days (range, 1 to 10 days) after the third monthly administration of LUNELLE. The average steady-state C_{max} for MPA was 1,254 pg/ml. MPA

levels gradually declined thereafter with a mean $t_{½}$ of 14.7 days, indicating that absorption from the injection site is prolonged after IM administration of LUNELLE. The time for MPA concentrations to fall below the LLOQ [redacted] after the third injection ranged from 63 to 84 days (the last scheduled PK sampling time point). The average trough (C_{min}, day 28) concentrations of MPA for the three consecutive monthly injections ranged from 437 to 469 pg/ml, indicating that steady-state conditions were achieved after the first injection. These C_{min} values were above the sponsor defined threshold MPA concentration that is expected to exert contraceptive effect.

Absorption of 17β-E_2 from the injection site was also prolonged after IM injection of LUNELLE (Figure 1B). Mean serum concentrations of 17β-E_2 peaked by 2.1 days (range, 1 to 7 days) after the third monthly injection, and the average C_{max} was approximately 247 pg/ml. Serum 17β-E_2 levels declined relatively faster than MPA with a $t_{½}$ of about 8 days; estradiol concentrations were at baseline values (typically ~ 100 pg/ml) by 14 days post injection. The average trough (C_{min}, day 28) concentrations for 17β-E_2 ranged from 40 to 55 pg/ml, further indicating that steady-state conditions are achieved after the first monthly injection.

Effects on total/free testosterone and dehydroepiandrosterone-sulfate (DHEA-S) were characterized by a high degree of intersubject variability. Mean serum values for these androgens measured prior to the second and third monthly injections of LUNELLE tended to be slightly lower than the corresponding values determined prior to the first dose (day 0, baseline). Furthermore, suppression of androgens appeared to be more pronounced during the first two weeks after LUNELLE administration. At this time, mean values for total and free testosterone declined by 38% (day 14 post third dose) while DHEA-S concentrations were reduced by more than 17% (day 7 post third dose). Thus, it appears that after LUNELLE injection, androgen levels steadily decrease by the second week post injection, then begin to recover thereafter but remain lower at the end of the injection interval. A temporal relationship is apparent between androgen suppression and elevated levels of MPA and/or 17β-E_2 following LUNELLE injection.

Mean values for sex hormone binding globulin (SHBG) measured prior to the second and third monthly injections of LUNELLE tended to be slightly lower than the corresponding values determined prior to the first dose. In contrast to androgens, SHBG showed tendency to increase within the first two weeks after LUNELLE injection and decline thereafter.

(ii) Pharmacodynamics:

Suppression followed by return of ovarian function (occurrence of ovulation) was assessed by measurement of serum levels of progesterone. Ovulation was confirmed by serum progesterone concentrations ≥4.7 ng/ml [Aedo 1985[1]]. Also, to determine the relationship between serum levels of MPA and pharmacokinetic parameter estimates with the return of ovulation, correlation analyses were performed.

[1] Aedo AR, Landgren BM, Johannisson E, Diczfalusy E. *Contraception* 31(5):453-69;1985.

After the third LUNELLE injection, serum progesterone concentrations were measured until demonstration of return of ovulation was observed. Serum progesterone concentrations were completely suppressed after LUNELLE injection in all 14 subjects. Consequently, ovulation was inhibited throughout the treatment period. The first normal ovulatory cycle (confirmed by serum progesterone concentrations ≥ 4.7 ng/ml) in 11 women was observed between days 63 and 112 post third injection. Three women were lost to follow-up before this objective could be achieved. Two women discontinued participation in the study.

For correlation of select pharmacokinetic parameters with ovulation, individual MPA AUC and the C_{min} values for the 11 women who returned to normal ovulatory cycles are plotted (Figures 2 & 3). Although coefficients of determination (R^2) are relatively low, there is a trend indicating that higher MPA AUCs may result in delayed return to ovulation following LUNELLE treatment. A temporal relationship is also apparent between the declining MPA levels (during the terminal elimination phase) and resumption of ovulatory progesterone peaks.

Comments:

- Three patients who were "lost to follow up" after 85 days had not returned to serum ovulatory progesterone levels as expected (till 85 days). This might potentially be a safety concern.
- Based on the fact that suppression and maintenance of the suppressed level of progesterone directly correlates with efficacy, it may be argued that C_{min} and $t_{½}$ are more relevant PK parameters related to efficacy of LUNELLE. The sponsor determined that 100–200 pg/ml were the threshold MPA levels for ovulation to remain suppressed during successive LUNELLE injections. The C_{min} values for MPA did not fall below that level.
- The 17β-E_2 (estradiol) levels following LUNELLE administration were within the normal range, but the plasma profile is different than what is presented (figure 1 of Label) as the "Plasma E_2 Hormone Profile of the Normal Menstrual Cycle".
- E_2 concentrations were not determined beyond day 28 post third injection.
- The observed metabolic changes in androgens and SHBG are characterized by a high degree of inter-subject variability with tendency to reduce serum androgens and slightly increase SHBG after LUNELLE administration.
- There was a trend (although weak based on R^2 of 0.58) that the higher the AUCs were for MPA, the higher was the delay for a "return to ovulation". This return to ovulation correlated very weakly with MPA C_{min} values and was considered to be insignificant (i.e., no real trend).

Study II: Protocol # M541S/0004

Objectives:

The objectives of this study were to determine:

1) The steady-state pharmacokinetics of MPA after administration of LUNELLE into the deltoid (arm), the gluteus maximus (hip), or the anterior thigh (leg). This comparison focused on the $AUC_{0\text{-}28d}$, C_{max}, C_{min} (day 28) and $t_{½}$ parameter estimates of MPA.

2) The effect of body mass index (BMI) on the steady-state pharmacokinetics of MPA. The PK parameters considered for this study were the same as above.

Study Design:

This was a multiple-dose and open-label trial. Four centers participated in the pharmacokinetic assessment. Each of the first three centers was assigned either the arm, hip, or the leg injection site without randomization, and the fourth center served as a backup for all injection sites. To ensure that each injection location receives at least two consecutive monthly LUNELLE injections, the centers were required to administer the study drug into the same anatomic location on the 5th, 6th, and if needed, the 7th monthly injections. Female volunteers (18-49 years of age), already enrolled in the Phase III clinical trial, were studied. Women had complete physical examination including, breast exam, pelvic exam with Pap smear, and provided complete medical history before acceptance into the trial. A total of 77 women completed the kinetic blood-sampling schedule and their data were analyzed. The effect of the injection site was determined with respect to the PK parameters. The data was re-analyzed following grouping the patients in 3 (initially) or 2 (finally) broad BMI categories, and the PK parameters were compared among those BMI groups.

Results & Conclusions:

The mean (±SD) serum MPA concentration-time plots are presented in Figure 4. Summary statistics for MPA concentration data and steady-state pharmacokinetic parameters by injection sites and BMI are provided in Tables 2 - 5.

The mean serum MPA concentration-time profile was higher when LUNELLE was injected into the deltoid (arm) compared with serum MPA profiles obtained after injection into the gluteus maximus (hip) and the anterior thigh (leg). Over the time course of 28 days, significant differences in mean MPA concentrations were observed on days 7, 14 and 21 between the arm and the leg injection sites; these differences ranged from 23% to 35% (Table 2). In contrast, the mean MPA concentration-time profiles appeared similar when LUNELLE was injected into the hip or the leg. The only significant difference in MPA concentrations between the hip and the leg injection sites occurred on day 14; the difference was approximately 24%. One subject in the leg group showed serum MPA concentrations approximately 6-fold higher compared to the rest of the group, resulting in variance differences on day 3 (sponsor believes that such deviation might have been due to interception of a major vein at the injection site resulting in a greater access of MPA into general circulation[2]). Exclusion of this subject from the statistical analysis (outlier) did not change the overall statistical outcome. The average MPA trough (C_{min}) concentrations on the fifth (day 0) or the sixth (day 28) monthly administration were similar when injections given either into the deltoid, the gluteus maximus, or the anterior thigh muscle. These C_{min} values ranged from 421 to 506 pg/ml. However, there was a significant difference in AUC_{0-28} between the arm and the leg injection sites and the difference was approximately 24%.

[2] According to facsimile received from sponsor dated 9/29/99 at our request.

When the patients were grouped into two broad BMI categories (BMI≤ 28 or >28) and ANOVA performed to compare the PK parameters (Table 5), both C_{max} and AUC_{0-28} were found to be significantly different ($p < 0.05$). An attempt was made to correlate the MPA AUC values following administration of LUNELLE to the arm, hip and leg to the BMI, and weak R^2 values were obtained (implying that the correlations were weak). Among those, the negative relationship between "leg AUC" and BMI was the strongest (Figure 5).

Comments:

- There was a significant difference in MPA AUCs between the arm and leg injection. Since results of the previous study (protocol # 0006) showed a correlation (although weak) between AUC and return to ovulation, switching injection sites may lead to unpredictable times required to return to ovulation post treatment.
- Although MPA C_{min} values were not presented for a PK comparison (Tables 2 – 5), review of the data shows that the C_{min} values remained above the threshold required for suppression of ovulation (efficacy).
- MPA AUC values differed between high and low BMI groups. Hence, difference in efficacy of LUNELLE might be observed between such groups. Dosage adjustment, however, is not recommended since C_{min} values remained above the threshold for efficacy.
- Combining effects of site of injection and BMI, caution should be exercised when a sufficiently light woman is injected LUNELLE in the arm. AUC values may rise high enough to significantly prolong a return to ovulation.

Formulations

It was verified with the Chemistry reviewer that there was no difference in the formulations used in the two clinical studies, and that the same formulation will be the "to-be-marketed".

Bioanalytical Methods

Medroxyprogesterone Acetate

Quantitation of MPA in human serum was conducted using a validated, sensitive and specific [redacted] method [Pearsall *et. al*[3]]. Inter-day precision values ranged from [redacted] Mean accuracy values were from [redacted] of the nominal concentrations of the calibration standards. Assay precision, expressed as %CV, averaged [redacted] and [redacted] for the [redacted] and [redacted] QC standards, respectively. Assay accuracy was expressed as the % ratio between the mean of the QC standard to the theoretical concentration of that standard. Accuracy values were from [redacted] of the

3 [redacted] 'Analytical Report, GC/MS Analysis of Medroxyprogesterone Acetate (MPA) in Human Serum", Project [redacted] dated 29 May 1998.

theoretical concentration for the three QC standards. No sample concentrations exceeded the range of the calibration curve.

Estradiol

For measurement of 17β-E_2, an [redacted] assay on the [redacted] was used. This was a [redacted]. Inter-assay precision, expressed as %CV, averaged [redacted] and [redacted] for the [redacted] QC standards, respectively.

Progesterone

For quantitative measurement of serum progesterone, another [redacted] assay on the [redacted] specific for progesterone was used. This method operates under the same principles as the estradiol method described above. Inter-assay precision, expressed as percent %CV, averaged [redacted] and [redacted] for the [redacted] and [redacted] QC standards, respectively.

Androgens

Total testosterone was measured by [redacted] kit. The antiserum is highly specific for testosterone. Crossreactivity to most other steroids and drugs is <3.5%. Inter-assay precision (%CV) averaged [redacted] and [redacted] for the [redacted] and [redacted] QC standards, respectively. The assay reference ranges were [redacted]

Sex Hormone-Binding Globulin

For measurement of SHBG, a commercial [redacted] kit was used. No human serum protein is known to cross-react with the antibodies used in this assay system. Assay sensitivity was [redacted]. Inter-assay precision, expressed as %CV, for [redacted] and [redacted] QC standards were [redacted] and [redacted] respectively.

Comments:

- A detailed bioanalytical method report was generated and submitted only for MPA. None were generated for the 17-β-E_2 or other analytes because (according to the sponsor) only MPA is related to efficacy (suppression of ovulation) and safety (return to ovulation) and the other analytes were primarily for scientific interest[4].
- Other than MPA, none of the methods originally reported a value for accuracy of the method. As much as the precision is important, without a value of accuracy, a method may not be deemed reliable. At our request, sponsor sent data reporting accuracy values between [redacted] for E_2 and [redacted] for progesterone[5].
- Based on the fact that most of the key judgements were made regarding the PK of MPA, the assay validation reports presented in the submission (and related communications) are acceptable, although not completely satisfactory.

[4] Facsimile received from sponsor dated 6/7/99 (containing analytical method validation data summary)
[5] Facsimile received from sponsor dated 9/29/99 at our request

Labeling Comments

The Medical Officer reviewing this submission has already modified the sponsor-proposed labeling for LUNELLE significantly. Please refer to this modified version of the label as attached. Specific comments on the Pharmacokinetics section are as follows. Suggested additions of text are highlighted. Deletions of text portions are indicated by ~~strikeout~~.

1. Page 3: Modified Table 1 is acceptable based on the results from study protocol # M/5415/0006. Note the correction on the top of the 4th column. It should read "AUC_{0-t}", instead of [redacted]

2. Page 3, line 83: After administration of LUNELLE, the range of E_2 concentration observed is comparable to that of normal preovulatory E_2 concentrations seen in fertile women. [redacted] The profile of E_2 following administration of LUNELLE is shown in figure 1.

3. Figure 1 is misleading, and should really be changed to the mean E_2 concentration profile seen following administration of LUNELLE, as obtained from study # M/5415/0006 (as in Figure 1B of APPENDIX attached herein). Alternatively, the sponsor may overlay the plot that is currently shown in the label (for normal cycles) with the profile they obtained from study # M/5415/0006 (Figure 1B). In case the sponsor chooses the latter, the second sentence of comment #2 may be suitably modified to reflect this overlay.

4. Page 3, line 97: ***Effect of Injection Site:*** [redacted] The mean MPA C_{max} was higher..... were not measured.

5. Page 4, line 121: ***Return to Ovulation:*** [redacted]

6. Page 4, line 128: ***Race:*** The pharmacokinetics of MPA and E_2..... studies. With the exception of one study in Thai women [redacted] relatively higher [redacted] values [redacted] both MPA [redacted] ..... backgrounds studied.

7. Page 5, Line 179: **Body Weight** – No dosage adjustment is necessary based on body weight. The effect of body ..... Phase 3 trial. [redacted] women with body mass index [redacted] when compared to that in heavier women with body mass index [redacted] The mean MPA C_{max} was.....both groups.

APPENDIX I

Table 1. Summary of Steady-State Pharmacokinetic Parameters of Medroxyprogesterone Acetate (MPA) and Estradiol (17β -E2) following the 3rd Monthly Injection of LUNELLE [Study M/5415/0006]

		C_{max} (pg/ml)	t_{max} (day)	AUC_{0-28} (pg·day/ml)	AUC_{0-84} (pg·day/ml)	$AUC_{0-\infty}$ (pg·day/ml)	$t_{1/2}$ (day)
MPA	Mean	1253.8	3.5	21511.0	32127.3	33651.2	14.7
	Median	1220.0	3	22115.3	34111.9	35381.1	12.8
	SD	327.7	2.9	3977.4	6255.7	7593.1	7.8
	N	14	14	14	14	14	14
	Min	[redacted]					
	Max						
17β-E2	Mean	247.1	2.1	2741.2	nd	2991.8	8.4
	Median	219.0	1.0	2651.5	nd	3071.4	7.3
	SD	97.3	1.9	556.9	nd	591.5	4.3
	N	14	14	14	nd	14	14
	Min	[redacted]					
	Max						

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Table 2. Mean (SD) MPA Concentrations (pg/ml) Following the Sixth/Seventh Monthly Administration of LUNELLE Stratified by Injection Sites [Study M/5415/0004]

Time (days)	Site of Injection			Analysis	
	A: Arm n = 27	H: Hip n = 23	L: Leg n = 27	ANOVA p-value	Multiple Comparison*
0	506.1 (187.1)	454.5 (167.9)	449.4 (152.5)	0.4118	A H L
3	1420.1 (361.6)	1293.2 (675.7)	1287.2 (1304.6)	0.8273	A H L
7	1141.0 (364.2)	1084.8 (389.9)	887.6 (282.9)	0.0260	A H L
14	877.9 (248.1)	803.7 (307.7)	648.1 (250.9)	0.0101	A H L
21	668.7 (159.5)	611.4 (179.0)	541.8 (236.8)	0.0663	A H L
28	474.1 (132.7)	474.3 187.5	421.4 (216.4)	0.4813	A H L

* Categories not connected by a line are significantly different at < 0.05

Table 3. Mean (SD) Pharmacokinetic Parameters of MPA Following the Sixth/Seventh Monthly Administration of LUNELLE Stratified by Injection Sites [Study M/5415/0004]

Parameters	Site of Injection			Analysis	
	A: Arm n = 27	H: Hip n = 23	L: Leg n = 27	ANOVA p-value	Multiple Comparison*
C_{max} (pg/ml)	1452 (362.9)	1362 (654.1)	1301 (1275.5)	0.8119	A H L
t_{max} (day)	3.7 (1.6)	4.3 (2.1)	3.9 (2.7)	0.7064	A H L
$AUC_{0\text{-}28}$ (pg.day/ml)	24491 (5710.7)	22817 (5980.5)	19672 (9005.7)	0.0478	A H L
λ_z (day^{-1})	0.04 (0.01)	0.05 (0.02)	0.04 (0.01)	0.5386	A H L
$t_{½}$ (day)	17.9 (8.6)	16.9 (6.5)	18.0 (5.9)	0.8418	A H L

* Categories not connected by a line are significantly different at < 0.05

Table 4. Mean (SD) MPA Concentrations (pg/ml) Following the Sixth/Seventh Monthly Administration of LUNELLE Stratified by Body Mass Index (BMI) [Study M/5415/0004]

Time (days)	BMI Category*			Analysis	
	A: 18-28 n = 48	B: > 28-38 n = 23	C: > 38 n = 6	ANOVA p-value	Multiple Comparisons†
0	510 (168)	423 (162)	350 (115)	0.0226	A B C
3	1529 (1030)	1035 (376)	1017 (326)	0.0519	A B C
7	1083 (328)	992 (414)	856 (361)	0.2706	B C A
14	816 (285)	716 (297)	701 (172)	0.3184	A B C
21	653 (209)	541 (163)	490 (139)	0.0270	A C B
28	482 (191)	433 (155)	332 (160)	0.1229	A B C

* All subjects were classified into three BMI categories: A 18-28, B >28-38 or C >38

† Categories not connected by a line are significantly different at < 0.05

Table 5. Mean (SD) Pharmacokinetic Parameters of MPA Following the Sixth/Seventh Monthly Administration of LUNELLE Stratified by Body Mass Index (BMI): Two BMI Categories [Study M/5415/0004]

Parameters	BMI Category*		Analysis
	A: <28 n = 48	B: > 28 n = 29	ANOVA p-value
C_{max} (pg/ml)	1,548 (1,004)	1,083 (388)	0.0197
t_{max} (day)	3.8 (2.2)	4.3 (2.1)	0.3304
AUC0-28 (pg.day/ml)	23,930 (7,540)	19,643 (6,225)	0.0123
λ_z (day^{-1})	0.04 (0.01)	0.04 (0.02)	0.7804
t½ (day)	17.0 (5.7)	18.8 (8.9)	0.2970

* All subjects were classified into two BMI categories: A≤28 or B>28

Figure 1A. Mean (SD) Serum Concentration-Time Profile of Medroxyprogesterone Acetate (MPA) Following the 3rd Monthly IM Injection of LUNELLE to Surgically Sterile Females [Study M/5415/0006]

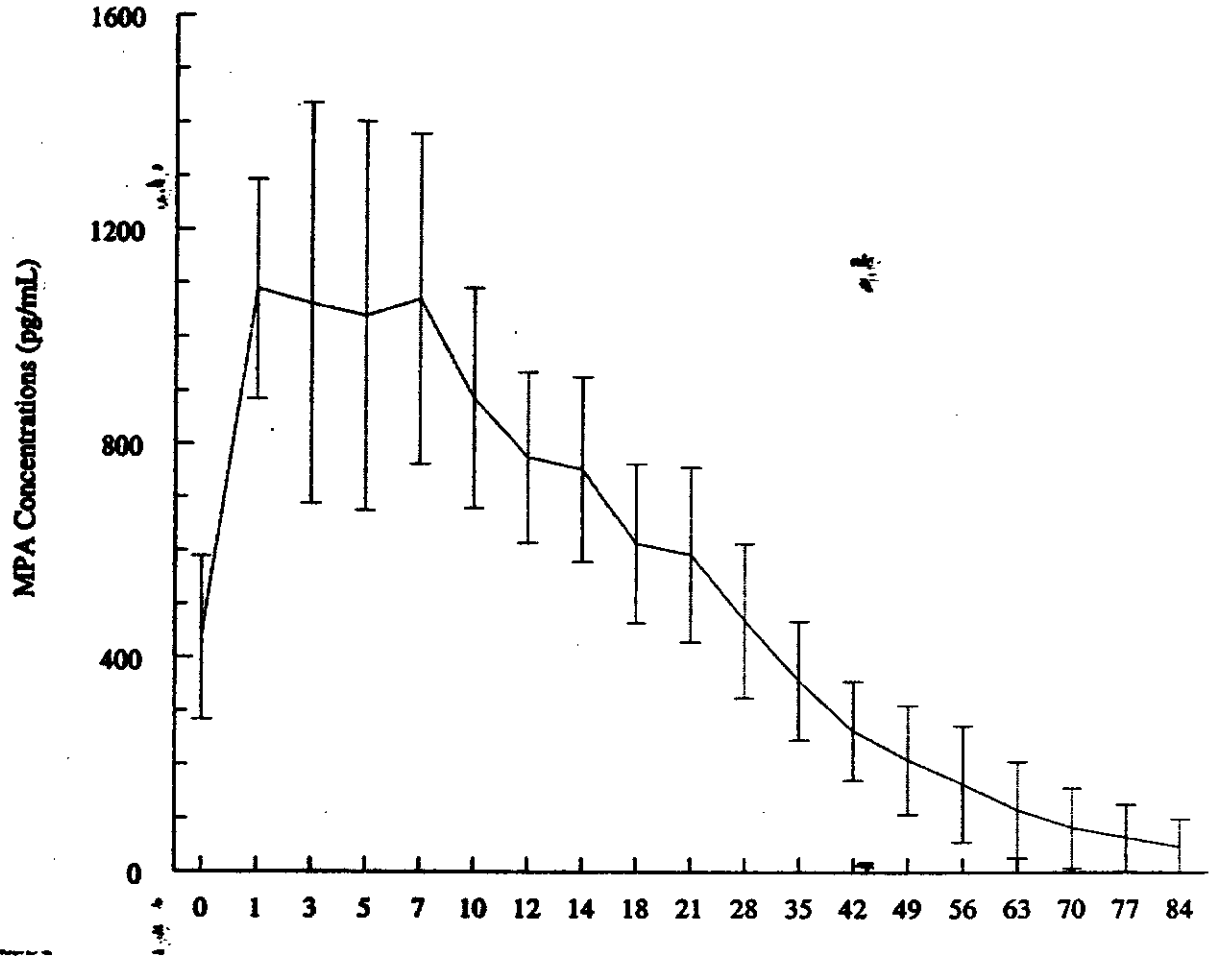

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Figure 1B. Mean (SD) Serum Concentration-Time Profile of Estradiol (17β-E2) Following the 3rd Monthly IM Injection of LUNELLE to Surgically Sterile Females [Study M/5415/0006]

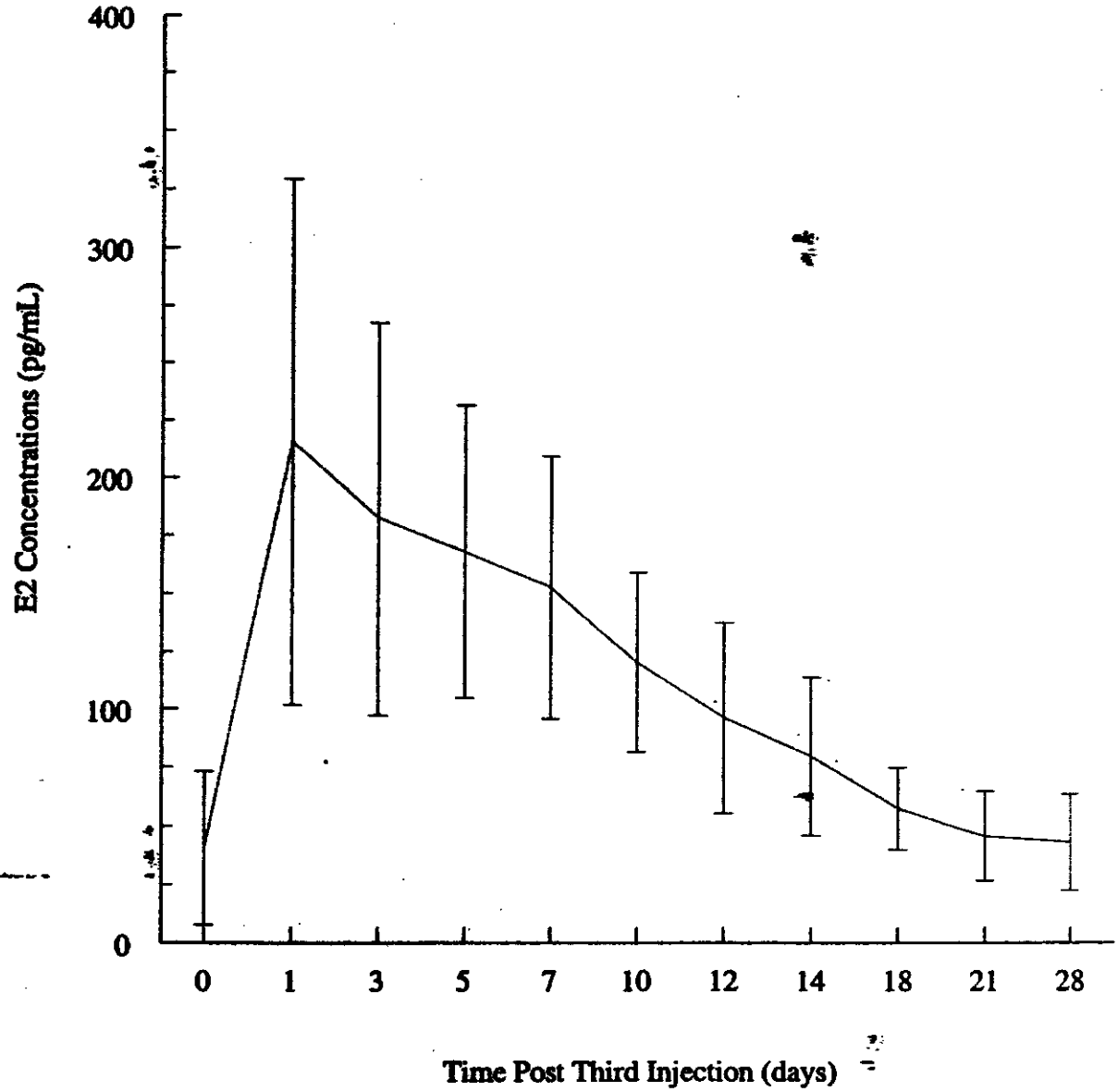

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Figure 2. Plots of MPA AUC0-84 vs Return of Ovulation (Days Post 3rd Monthly Injection of LUNELLE for the 11 PD-Evaluable Subjects [Study M/5415/0006]

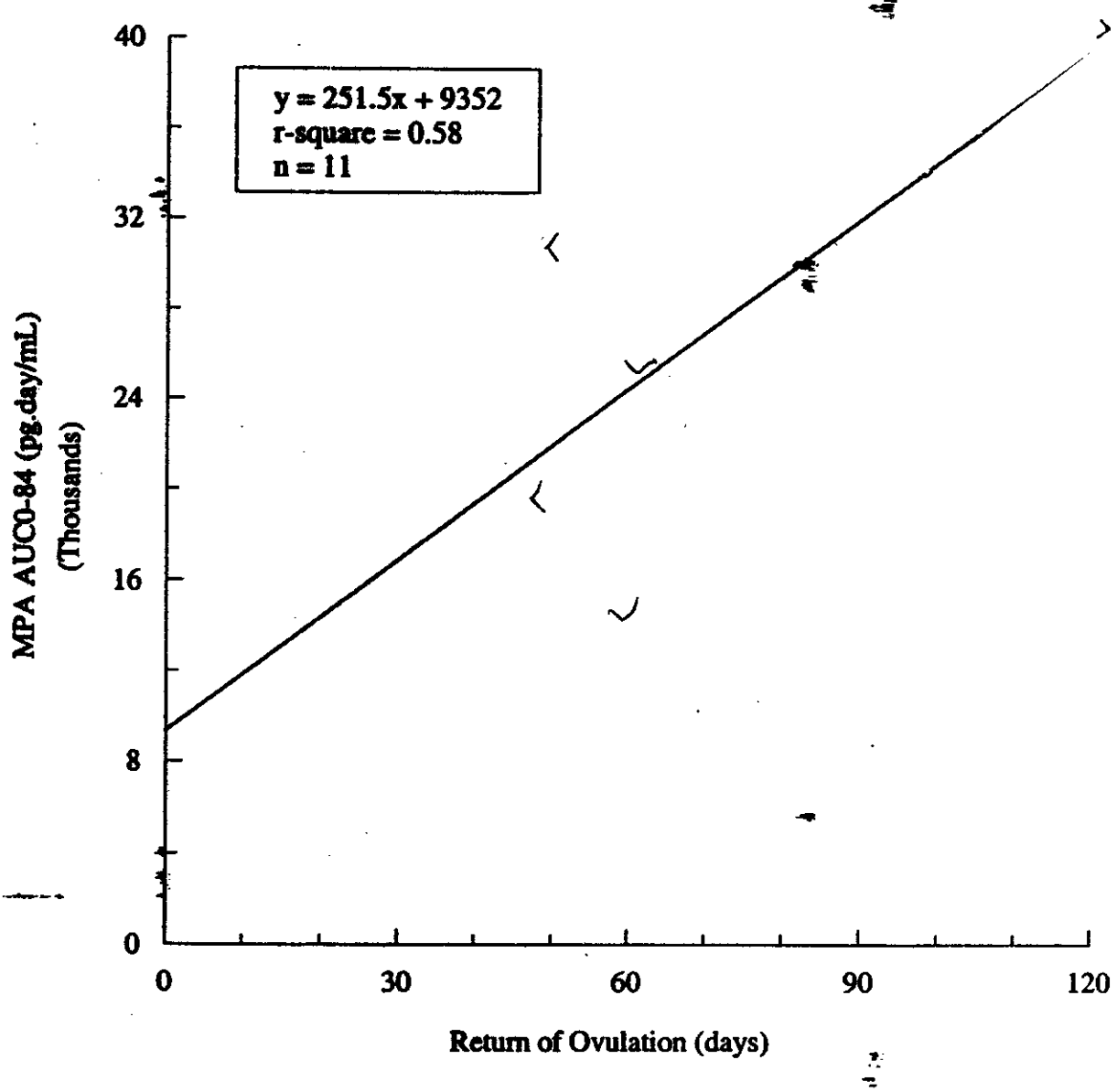

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Figure 3. Plot of MPA Cmin (Concentrations at Day 28 Post 3rd Injection) vs Return of Ovulation (Days Past Day 28 of Last Injection) Following LUNELLE for the 11 PD-Evaluable Subjects [Study M/5415/0006]

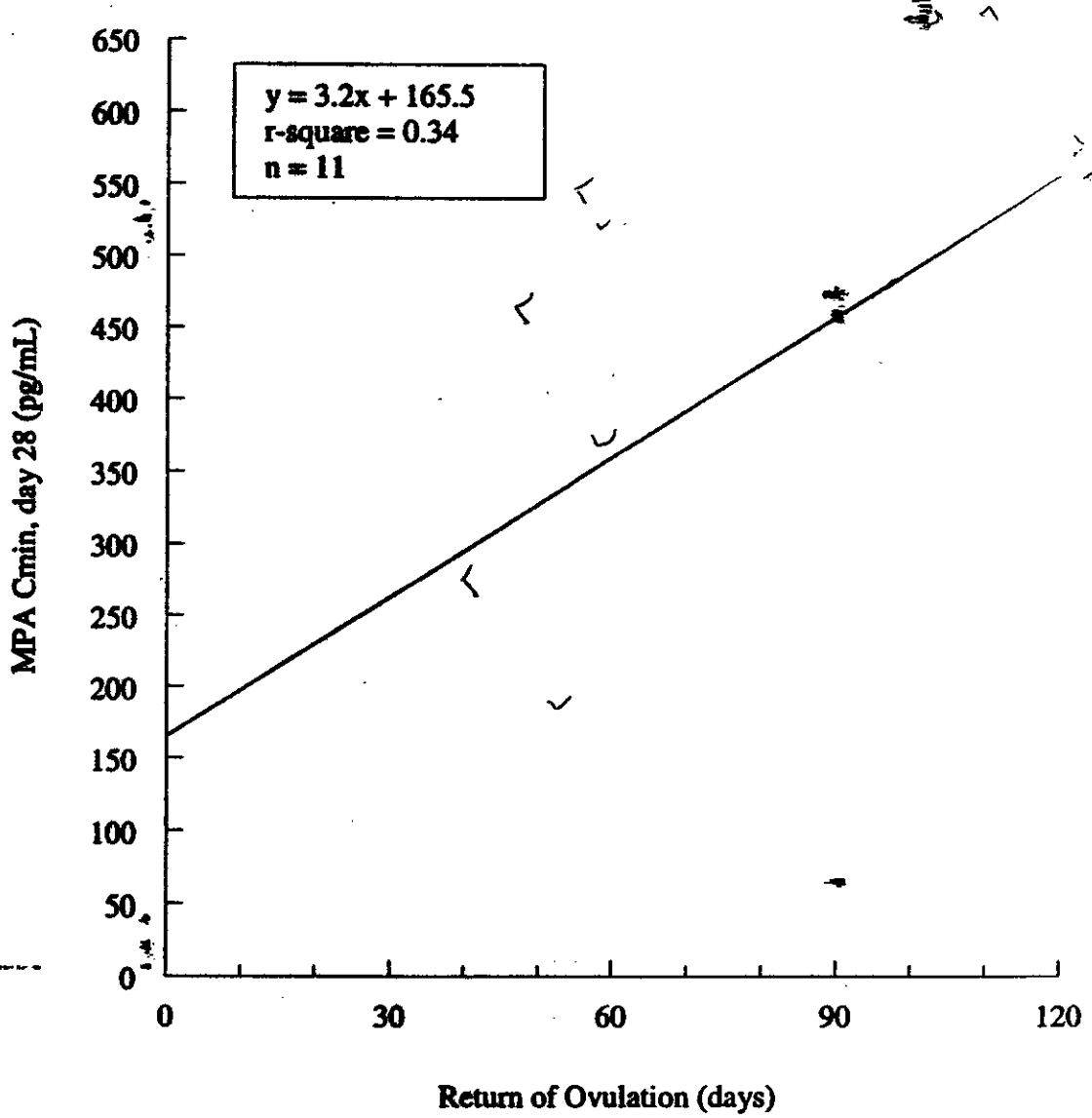

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Figure 4. Mean (SD) Serum MPA Concentration-Time Profile Following the Sixth/Seventh Monthly IM administration of LUNELLE by Injection Sites [Study M/5415/0004]

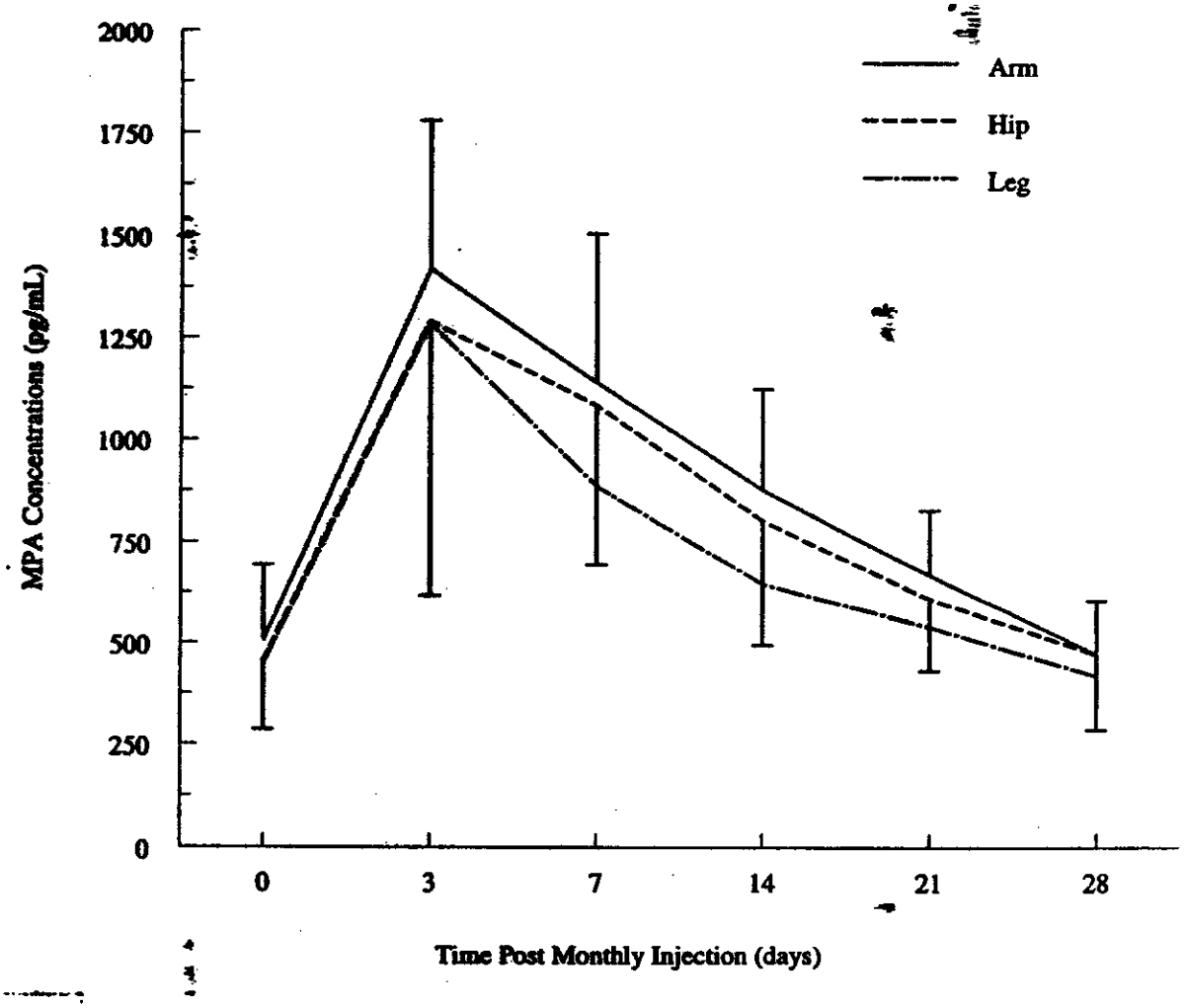

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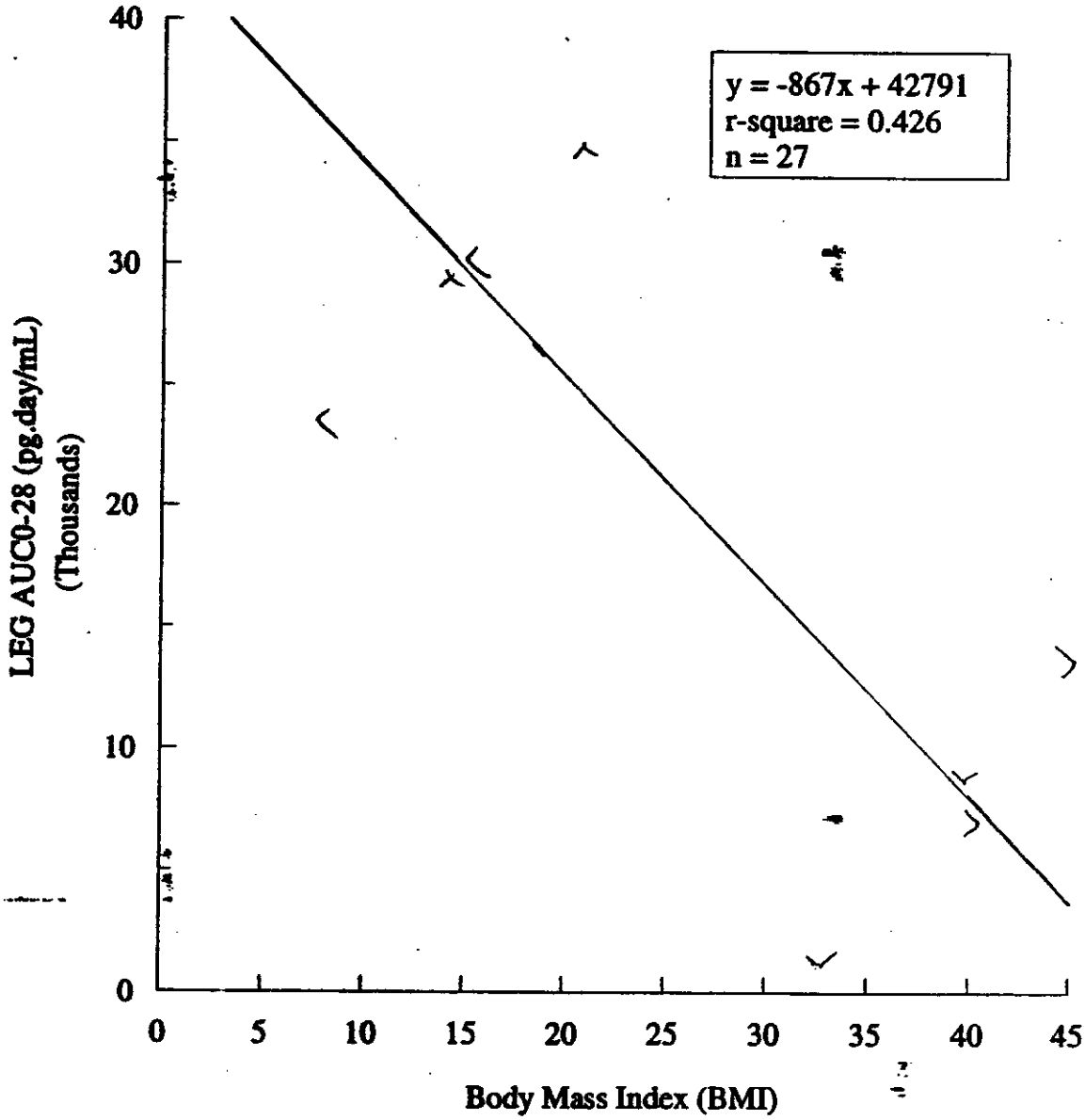
Figure 5. Plot of MPA AUC vs BMI for the 27 Women Receiving the Sixth/Seventh Injection of LUNELLE in the Anterior Thigh (Leg) [Study M/5415/0006]



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APPENDIX II

Angelica Dorantes's Review of NDA 20-874 (Original Submission)

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AUG -6 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA	20-874 (NC)
SUBMISSION DATE:	7/28/98
PRODUCT/GENERIC NAME:	Esprova® (Cyclo-Provera, medroxyprogesterone acetate, MPA, and estradiol cypionate injection)
SPONSOR:	Pharmacia & Upjohn
TYPE:	Response to Questions
REVIEWER:	Ameeta Parekh, Ph.D.

Background: This application is an amendment to the NDA 20-874 under review for monthly contraceptive injection. Several questions were raised by the medical and the clinical pharmacology/biopharmaceutics reviewers. The information (question #s 7, 10, 15) related to pharmacokinetics (pk) and ovulation in relation to body weight and body mass index (BMI) was requested and has been addressed in this amendment.

Comments: Based on the summarized data submitted by the sponsor, the following observations were noted:

a) The 77 women who completed the pk sampling were categorized into BMI categories of 18-28 (A), 28-38 (B) and >38 (C). Following the 7th monthly application, the MPA concentrations (pg/ml) showed a trend towards lower concentrations with higher BMI, as follows:

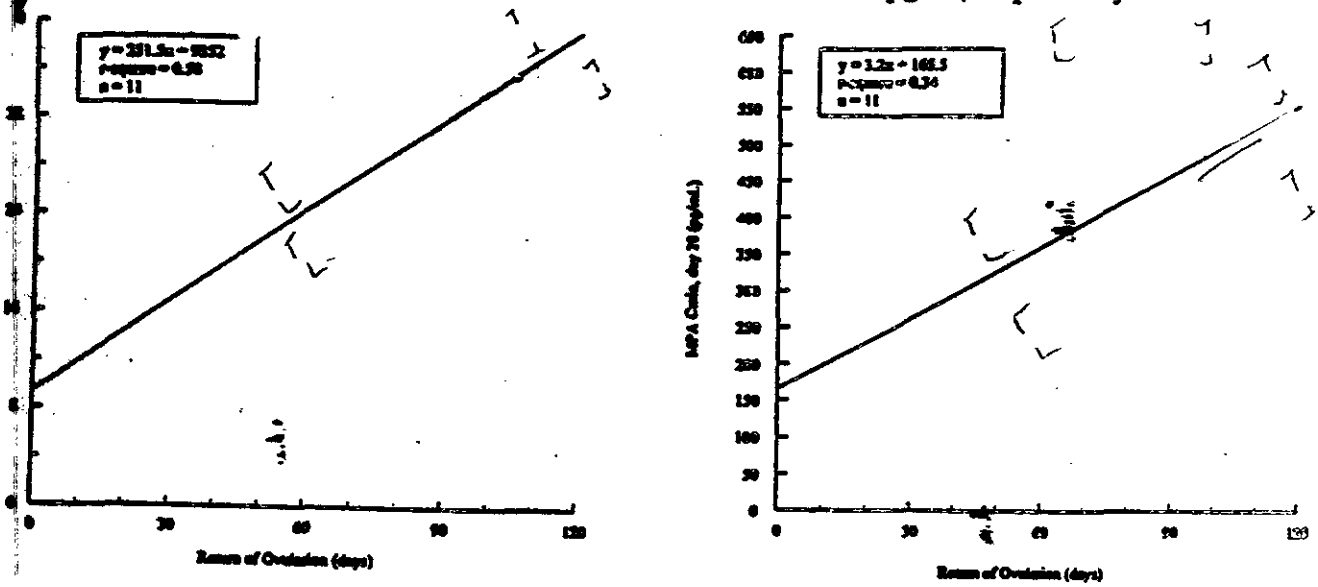
Day	A	B	C
0	510	423	350
3	1529	1035	1017
28	482	433	332

b) The pk summary submitted by the sponsor indicated a similar trend:

	Body Mass Index Category			Analysis	
Parameters	A: 18-28 n = 47	B: > 28-38 n = 22	C: > 38 n = 6	ANOVA p value	Multiple Comparison*
Cmax (pg/mL)					A B C
tmax (day)					A B C
AUC_{0-28} (pg.day/mL)	23,929.9 (7,539.9)	19,996.4 (6,604.4)	18,289.9 (4,724.6)	0.0387	B C A
t½ (day)	17.0 (5.7)	18.2 (6.2)	20.8 (16.1)	0.4340	A B C

* Categories not connected by a line are significantly different at < 0.05

c) The sponsor provided data on return to ovulation related to MPA AUCs and Cmins for only 11 subjects (they call these 'evaluable subjects'). This limited data shows ovulation at about 60 days with AUC and Cmin of 20 pg.days/ml and 200 pg/ml, respectively.



Recommendation: The information provided by the sponsor was discussed with the medical officer (Dr. Safran). No further action is indicated until the submission of study M/5415/0006 which is expected to address further safety and efficacy of this product. The sponsor noted that the report for this study will be completed in a week.

/S/ 8/6/98

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

FT signed by John Hunt, B.S. Deputy Director 8/6/98

cc: NDA 20-874; HFD-580 (Kish, Safran), HFD-870 (Dorantes, M.Chen), CDR (B.Murphy)

DF

JUL 1 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 20-874

SUBMISSION DATE: September 26, 1997
& November 24, 1997

CYCLO-PROVERA™ Contraceptive Injection
Medroxyprogesterone Acetate and Estradiol Cypionate
Pharmacia and Upjohn
Kalamazoo, MI

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Review of a New Drug Application

SYNOPSIS:

On September 25, 1997, Pharmacia & Upjohn submitted NDA 20-874 for Cyclo-Provera™ Contraceptive Injection. On November 24, 1997 a revised version of the NDA was submitted. Cyclo-Provera™ consists of 25 mg medroxyprogesterone acetate (MPA) and 5 mg estradiol cypionate (E2C) formulated as an aqueous microcrystalline suspension which is given in a 0.5 mL injection. Cyclo-Provera™ is a once monthly, intramuscular injectable contraceptive.

To support the "Human Pharmacokinetic and Biopharmaceutics" section of the NDA, the sponsor provided data from 11 pharmacokinetic and/or pharmacodynamic studies published in the literature from 1978 through 1995. These references present bio-studies covering different pharmacokinetic and pharmacodynamic issues (i.e., single and multiple dose administration, bioavailability, bioequivalence, dose proportionality, PK/PD, etc.). The validation of the RIA methods used for the quantitation of MPA in the published articles is incomplete or not provided. Therefore, lack of reliable assay information makes included pharmacokinetic information questionable.

At best, from a "qualitative" perspective, the data presented in the filed references indicate that:

MPA

- Following monthly injection of Cyclo-Provera, peak MPA concentrations are achieved in 7 to 10 days and the mean maximum MPA concentration after the third monthly injection is 1.12 (0.93-1.43) ng/mL and Cmax generally ranges from ——— after repeated monthly injections for one year.
- Low but measurable accumulation of MPA is observed after repeated monthly injections. MPA C_{max} and AUC_{0-28d} increase by 47% and 71%, respectively, from the first to the sixth injection of Cyclo-Provera indicating that MPA absorption from the injection site extends beyond 30 days. No further increase in MPA serum levels is noted from the 6 through the 12 monthly injections.
- Following discontinuation of Cyclo-Provera dosing, MPA concentrations remain detectable for up to approximately 60 days post-injection.
- MPA apparent half-life is 10-14 days.

E2C

- Absorption of estradiol (parent active moiety of E2C from the injection site is also prolonged after IM injection of Cyclo-Provera, but it appears to be more rapid than that for MPA.
- Serum E2 concentrations peak approximately 4 days post-injection and generally range 200-400 pg/mL.
- The peak serum concentrations observed after Cyclo-Provera administration are similar to the normal preovulatory E2 concentrations seen in healthy fertile women.
- Unlike MPA E2 does not accumulate after repeated monthly injections in women followed up to 1 year.
- Serum E2 levels decline to basal levels (<100 pg/mL) by day 14.
- E2 apparent T1/2 is 4-7 days.

Ethnic Differences:

- The pharmacokinetics of MPA and E2 were evaluated in women from different countries (races) in which Cyclo-Provera was investigated. With the exception of Thai (Asian) women, serum MPA and E2 concentrations following Cyclo-Provera administration were similar in women from various countries.
- Thai women show relatively higher Cmax and shorter Tmax values for both MPA and E2, indicating faster drug absorption following Cyclo-Provera administration.
- The contraceptive efficacy of Cyclo-Provera was similar in Thai women compared to other populations, however, reversal of the contraceptive effect appears to be established earlier in Thai women, consistent with the PK differences observed.

Pharmacodynamics:

- PD studies show that monthly administration of Cyclo-Provera consistently inhibits ovulation and corpus luteum formation, beginning in the first injection cycle at the recommended dose of 25 MPA/5 E2C mg. Ovulation is not consistently suppressed at lower doses (12.5 MPA/2.5 E2C mg or 12.5 MPA/5 E2C mg).

REVIEWER COMMENT:

- It should be noted that on May 2, 1997, Pharmacia & Upjohn Co. submitted Amendment Serial No. 004 to IND 52,624 which included Protocol No. M/5415/0006 for a study entitled ***"CYCLO-PROVERA™ Contraceptive Injection: A Pharmacokinetic and Pharmacodynamic Study After Repeated Aministration (3 monthly doses) in Surgically Sterile Females"***. The objective of this study was to characterize the PK and PD (return to ovulation) of MPA and E2 after repeated administration of Cyclo-Provera (the to-be-marketed formulation and validated assays were used). On June 29, 1998 the sponsor indicated that this study has been completed and the final report will be submitted by end of July 1998.

OMMENDATION:

he Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the referenced articles provided by the sponsor for Cyclo-Provera (original NDA 20-874 filed on September 26, 1997 and revised version filed on November 24, 1997). Based upon the review of the submitted information, OCPB/DPEII can not draw strong conclusions as to the accuracy of the submitted reference articles regarding the pharmacokinetic characteristics of MPA and estradiol because no reliable validation information for the analytical methods used in the published studies was provided. Considering that the sponsor has recently completed Study M/5415/0006 (a new PK/PD study that used to-be-marketed formulation and validated assays) that will be submitted in July 1998, it is felt that information from this study is important to support the approval of Cyclo-Provera. Therefore, OCPB/DPEII is of the opinion that a final recommendation for this NDA would be given after review of the additional data. However, if the Medical reviewers of HFD-580 (Drs. Julian Safran and Susan Allen) feel that there are no safety/efficacy concerns and the product is approvable, then the additional information could be submitted as a Phase IV Commitment within 3 months of approval date.

For the proposed package insert of Cyclo-Provera™ Contraceptive Injection, it is acceptable, provided the changes that are proposed are incorporated into the pharmacokinetic section of the package insert. After the labeling is modified, the firm should resubmit the package insert for its review. In addition, the package insert should be further updated based upon the new PK/PD information that is to be submitted.

Please convey the Recommendation as appropriate and Labeling Comments (pages 22 and 24) to the sponsor.

NOTE: Attachment I to V are being retained in OCPB and may be obtained upon request.

CD 6/30/98

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD Initialed by John Hunt. JPH 6/30/98

FT signed by John Hunt. /S/ 7/1/98

cc: NDA 20-874, HFD-580 (Safran, Allen, Kish), HFD-870 (Chen, Dorantes), CDR. (Barbara Murphy for Drug).

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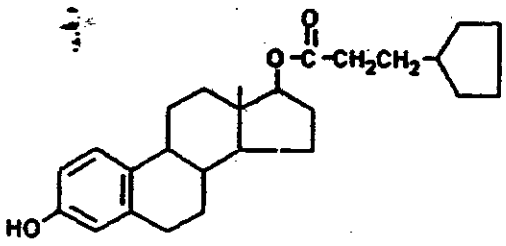
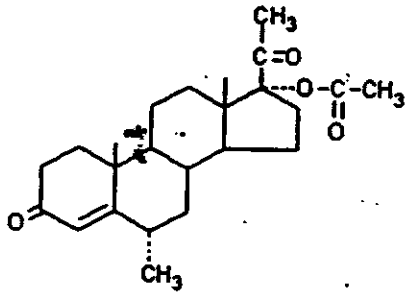
III. BACKGROUND:

Cyclo-Provera Contraceptive Injection is an aqueous suspension of 25 mg MPA and 5 mg E2C. MPA is a derivative of progesterone and E2C is an ester of 17β-estradiol. The drug delivery rationale of Cyclo-Provera is to provide low but stable serum concentrations of MPA for approximately one month and E2 for two weeks after monthly intramuscular administration. Based on this strategy, it is presumed that MPA would suppress ovulation for at least one month and thereby provide a contraceptive effect, while E2C would mimic normal preovulatory surge of E2, thus leading to regular monthly bleeding patterns. The structural formula and molecular weight of MPA and E2C are presented below:



Estradiol Cypionate (E2C)

($C_{26}H_{34}O_3$) molecular weight: 396.57



Medroxyprogesterone Acetate (MPA)

($C_{24}H_{34}O_4$) molecular weight: 386.53

IV. DRUG FORMULATION

Cyclo-Provera is a sterile aqueous suspension of medroxyprogesterone acetate and estradiol cypionate. The to-be-marketed formulation contains MPA and E2C at concentrations of _____ respectively. Two different strengths of the suspension were used in the 3 pivotal clinical studies. The two formulations are presented in Table 1. Specific information regarding the Cyclo-Provera formulations, batches/lot numbers used in each of the human pharmacokinetic/pharmacodynamic studies is included in Attachment I.

TABLE 1

Estradiol Cypionate Medroxyprogesterone Acetate		
Inactive Ingredients		
Methylparaben		
Propylparaben		
Sodium Chloride		
Polyethylene Glycol		
Polysorbate 80		
water for injection		

* Used in the Multicountry Study (No. 83913)
**Used in the Egypt (No. 88911) and China (No. 87903) Studies

From the theoretical perspective, bioavailability differences could potentially occur when formulations which differ with respect to the concentration of active ingredients, are injected intramuscularly. Because of concentration differences, the volume of injected suspension may also influence the bioavailability of the injected drug. Therefore, the sponsor provided solubility information to demonstrate that the two formulations of MPA and E2C used in the clinical trials are comparable with respect to prolonging the absorption of MPA and E2C after IM administration. Table 2 summarizes the results of the solubility determinations for MPA and E2C obtained from samples prepared 4.5 hours to 13 days prior to assay.

TABLE 2

0.5-mL Formulation	MPA — mg/mL	—	—	—	—
0.5-mL Formulation	E2C — mg/mL	—	—	—	—
1-mL Formulation	MPA — /mL	—	—	—	—
1-mL Formulation	E2C mg/mL	—	—	—	—

A formal in vivo study to demonstrate bioequivalence of the 2 different formulation strengths was not performed. However, a cross-study comparison of the pharmacokinetic data following injection of the 0.5 or 1.0 mL strengths suggests that drug absorption of MPA and E2 is relatively comparable with formulation. Table 3 presents the comparison of MPA and E2 pharmacokinetic parameters in women receiving 25 mg MPA: 5 mg E2c as 1.0 ml or 0.5 ml injections.

TABLE 3

Fotherby 1982 Four-country study (n=11)	1.0		200	1-10	NR	70	1-4
Asdó 1985 Sweden (n=8)	0.5 mL		278	4-5	11	56	4
WHO 1987 Mexico (n=8)	0.5 mL		NR	7.8	15.4	NR	3

NR= No reported

Table 4 summarizes the pharmacokinetic parameters for the 3 published studies that used the to-be-marketed formulation.

TABLE 4. SUMMARY OF MPA AND E2C PHARMACOKINETIC PARAMETERS

			Medroxyprogesterone Acetate			Estradiol	
			Cmax (ng/mL)	tmax (days)	t1/2 (days)	Cmax (pg/mL)	tmax (days)
WHO 1987a	Cyclo-Provera q 28d for 3 mo	0.5 mL	Mexico 1.5 Thailand 3.6	Mexico 7.8 Thailand 12.1	Mexico 15.4 Thailand 12.1	Mexico 184 Thailand 736 Hungary 202	Mexico 3 Thailand 2 Hungary 3
Sang 1995c & 1998	Cyclo-Provera 9 mo for 2 y: samples after 1st, 6th, and 12th injections	0.5 mL	1st 1.5 (0.5) 6th 2.1 (0.7) 12th 2.2 (0.7)	1st 3.4 (0.9) 6th 4.3 (2.2) 12th 3.7 (2.6)	ND	ND	ND
Aedo 1985	Cyclo-Provera q 30d for 3 mo	0.5 mL	1.1	ND	ND	242	4

ND= No Determined

COMMENTS:

1. Overall, the results indicate that the solubilized amounts of MPA and E2C in both formulations are insignificant when compared to the amount of total MPA and E2C injected. Therefore, following injection of either 0.5 mL or 1.0 mL formulation, it would be expected that the soluble aqueous components would be relatively quickly absorbed from the injection site and the unsoluble active components would remain as drug depot from which prolonged absorption resulting from low dissolution at the injection site would occur.
2. Based on the above solubility and pharmacokinetic data, systemic absorption of MPA and E2C from the injection site would be expected to be similar, regardless of whether it is given as a 0.5 mL or 1.0 mL formulation.
3. The pharmacokinetic data obtained from the 3 published studies reveled that absorption of both MPA and E2C was prolonged in a similar manner from either formulation.

V. ANALYTICAL METHODS

The radioimmunoassay (RIA) methods used in the pharmacokinetic and pharmacodynamic studies for the analysis of MPA, E2, and progesterone (P) were obtained from the published literature. However, assay validation reports for specific studies or methods are not available. For metabolic studies, MPA metabolites in plasma of long-term, high-dose MPA-treated patients were identified using — or HPLC separation and structural analysis by MS and ' —Selected MPA metabolites were determined by HPLC with UV detection. Attachment II includes a summary of the bioanalytical aspects of the analytical methods used in 7 of the PK/PD studies.

COMMENTS:

1. Validation information for the analytical methods used in the published studies is not available.

2. It should be noted that the samples were assayed using different methods and different laboratories. This may have contributed substantially to the reported inter-study variations in serum/plasma levels of steroid and non-hormones analyzed in the studies.

VI. PROTEIN BINDING INFORMATION

MPA: The in vitro protein binding of [3H]-MPA in fresh human plasma by equilibrium dialysis was assessed (Meyer-Statham, 1981). The results showed that more than 85% of MPA in plasma was present in the bound form with an apparent association constant of 2.6 x 104L/mol. MPA binding occurred primarily to serum albumin; no binding of MPA with other proteins was evident (i.e., SHBG).

E2C: Natural estrogens circulate in plasma bound to albumin, SHBG, a1-glycoproteins, and transcortin. Estradiol is loosely bound to albumin (low affinity/high capacity), but 1/3 of E2 in plasma is tightly bound to SHBG (high affinity/low capacity) and a low percent is free (<3%). The production of SHBG is stimulated by increasing estrogen concentrations. Because of the high concentration of albumin (approximately 5 times higher that of SHBG) and the rapid dissociation, albumin may serve a more important protein-binding role than SHBG (Wagner 1978 and Ingram 1990).

VII. METABOLIC INFORMATION

Metabolic studies have not been conducted with Cyclo-Provera. However, metabolism of MPA and E2C has been reported in the literature.

MPA: Medroxyprogesterone is a derivative of progesterone. The biotransformation of MPA following IM administration may differ from that of progesterone because of the shielding effects of the 6α-methyl and 17α-acetoxy groups on MPA molecule. The overall effect is decrease of the rate of metabolism of MPA, and prolongation of its biological activity, relative to progesterone (Gupta 1977).

MPA is extensively metabolized. Sixteen metabolites of MPA have been identified in plasma of long-term, high-dose MPA-treated patients (Strum 1991). MPA metabolites (primarily unconjugated forms) were identified using ' —or HPLC separation and structural analysis by MS and ' — Also, metabolites were detected in plasma samples of patients treated with MPA using an HPLC/UV method. The main routes of MPA metabolism appear to be ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation preferentially in the 2-,6-, and 21-positions or a combination of these positions, resulting in numerous derivatives. Hydroxylation in the 2-position can be followed by reduction of the 3-keto group or by dehydration.

The routes of MPA excretion appear to be quantitatively similar after oral or IM administration of the drug. Most MPA metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates. The extent to whic MPA is excreted in urine is about 44% in humans, after both oral and IM administration of MPA.

E2C: Estrogen esters such as E2C are metabolized in the body similar as the endogenous estrogens. After IM administration of Cyclo-Provera, E2C is slowly absorbed from the injection site over 1 to 2 weeks. In the general circulation, E2C undergoes ester hydrolysis, releasing the parent, active compound, E2, into the pool of estrogens. Inactivation of E2 occurs mainly in the liver. In fertile women, estradiol is primarily metabolized to estrone and estriol, both of which are metabolized to their sulfate and glucuronide forms, as well as oxidized to nonestrogens. Only 5% of estrone in blood is converted to E2, and no more than 1.4% of estrone-sulfate is converted to E2. Therefore, the overall fate of E2 is toward metabolism into estrone and estrone-sulfate (Lievertz 1987).

Estrone sulfate is the largest component of the estrogen pool in the body and serves as the reservoir primarily for estrone production and the predominant intracellular estrogen, which is estradiol. In the target population, production and clearance of endogenous estrogens depend greatly on the stage of the menstrual cycle. Under normal conditions there is low cellular enzymatic activity of 17β-dehydrogenase, which favors the conversion of estrone to estradiol. However in the luteal phase endometrium, this enzymatic activity increases and more estrone is produced which in turn is conjugated to estrone sulfate. Estrone sulfate is then available to enter the serum pool. Serum estrone sulfate can be selectively taken up by tissues (i.e., breast) and hydrolyzed to release estrone which, in turn, is converted to estradiol the most biologically active estrogen (Fotherby 1983 and Lievertz 1987). A proportion of estrogens is excreted into the bile and then reabsorbed from the intestine. During enterohepatic re-circulation, degradation of estrogens occurs through conversion to less active products such as estriol, nonestrogenic substances and sulfate and glucuronide conjugates.

VIII. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTIC STUDIES

A comprehensive reference list of the submitted published references is included in Attachment III. The pharmacokinetic and pharmacodynamic information included in this submission to support the approval of Cyclo-Provera is from published literature reports dated 1978 through 1995. Table 4 presents a summary of the clinical pharmacology and biopharmaceutic studies conducted with Cyclo-Provera.

TABLE 4. SUMMARY OF CLINICAL PK and PD STUDIES WITH CYCLO-PROVERA

Aedo 1985	Multiple-Dose & PK/PD	Cyclo-Provera	0.5 mL	q 30 for 3 mo	8 White	34-38
Bassol 1995	PK/PD	Cyclo-Provera	1 mL	120d follow-up after q 30± 3 d for ≥2 y	10 Hispanic	-
Fotheby 1982	Multiple-Dose & PK/PD	Cyclo-Provera	1 mL	q 28 d for 3 mo	5 White, 6 Hispanic	24-39
Garza-Flores 1989	Multiple-Dose	Cyclo-Provera	0.5 mL	blood sampled after single dose following>1 year of use	21 Hispanic	25 (mean)
Goldenstein 1974	Multiple-Dose	Cyclo-Provera	0.5 mL	follow-up after q 28±4 d for 33 mo	395 White	14-50 28.7 (mean)
Koetsawang 1978	Single-Dose	Cyclo-Provera Cyclo-Provera	0.5 mL 0.5 mL	q 28 d for>2 y single injection	111 Asian 5 Asian	20-29
Koetsawang 1979	Multiple-Dose	Cyclo-Provera Cyclo-Provera	0.5 mL 0.5 mL	31-45 injections at 28-d interval single injection	21 Asian 10 Asian	- -
WHO Study-A Sang 1994 Bassol 1994 Garza-Flores 1991	Dose -Proporti	12.5 mg MPA/ 5 mg E2C	-	q 30 d for 3 mo; 2 mo follow up	8 Asian 7 Hispanic 9 White	-
WHO 1987a	Dose -Proporti & Race	Cyclo-Provera 12.5 mg MPA/ 2.5 mg E2C	0.5 mL 0.5 mL	q 28 d for 3 mo q 28 d for 3 mo	22 A, H, W 22 A, H, W	- -
Sang 1996 & 1995c	Multiple-Dose	Cyclo-Provera	0.5 mL	q 30±3 d for 1 y; blood sampled on specific d after 1st, 6th, and 12th inj	9 Asian	18-35
Sturm 1991	MPA-Metabolism	MPA	-	Study of MPA metabolites	-	-
Mathrubutham 1981	MPA- Protein binding	MPA 150 mg	-	Binding of [3H]-MPA to albumin	9 Asian	-

1. BIOAVAILABILITY/BIOEQUIVALENCE:

a) Bioavailability:

A formal assessment of the absolute or relative bioavailability of Cyclo-Provera was not performed.

b) Bioequivalence:

A formal assessment of the 2 formulations used in the clinical and pharmacokinetic studies was not conducted.

2. PHARMACOKINETICS

a) *Single Dose Studies*

Koetsawang 1978: Serum concentrations of MPA after a single injection of Cyclo-Provera were determined by RIA in 5 Thai (Asian) women. Serum concentrations of MPA were measured before injection (baseline) and at 3 or 4, 7, 14, 21, 28, 42, and 56 days postinjection of 25 mg MPA:5 mg E2C in 0.5 mL. Serum E2 was not measured in this study. After Cyclo-Provera administration, serum MPA concentrations gradually increased. Individual maximum MPA concentrations (Cmax) ranged from [redacted], and Tmax ranged from 4 to 28 days. Serum MPA levels declined slowly by day 56 postinjection. MPA concentrations were 2.3-3.3 ng/mL on day 7, 1.4-3.5 ng/mL on day 28, and 0.6-0.9 ng/mL on day 56. The results of this small study indicated that absorption of MPA was prolonged following IM injection of Cyclo-Provera. Extensive variation in MPA concentrations among subjects was observed.

b) Multiple Dose Studies:

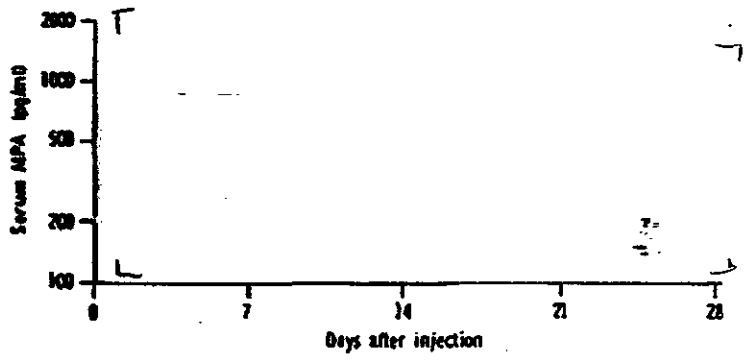
Pharmacokinetics of MPA:E2C after multiple doses were determined in 5 studies [Aedo 1985, Fotherby 1982, Garza-Flores 1989, Koetsawang 1979 and Sang 1995c/ 1996]. In the first 4 studies, serum/plasma concentrations of MPA and/or E2 were measured without pharmacokinetic data analysis, while in the remaining 2 studies, basic pharmacokinetic parameters were also estimated.

Koetsawang 1979: In this study, mean serum levels of MPA were determined in 31 Thai (Asian) women who had received single or multiple injections of Cyclo-Provera as follows: 1) a single injection (n = 10); and, 2) 31 to 45 injections at 28-day intervals (n = 21). Blood samples were taken 28 days after the single injection (group 1) or 28 days after the last injection (group 2). The results showed that after single or multiple injections of Cyclo-Provera, the mean (SEM) concentration of MPA was 1.03 ng/mL (0.05) or 1.32 ng/mL (0.07) at the end of the injection interval (day 28), respectively. Serum MPA levels were higher after 31 to 45 injections of Cyclo-Provera compared with after a single injection, suggesting that MPA accumulates with repeated monthly dosing. Wide intersubject differences in MPA concentrations were observed at the end of the injection interval.

Garza-Flores 1989: Serum E2 concentrations were measured in Hispanic women in a long-term study designed to evaluate effects of monthly injectable contraceptives on serum prolactin. The women (n = 21) received one dose of Cyclo-Provera after 1 year of monthly use of an estrogen-progestin contraceptive or an intrauterine device. Serum E2 levels were measured on day 0 and on days 10, 20, and 30 after the last monthly injection of Cyclo-Provera. Serum E2 concentrations were also measured in a control group of women using intrauterine devices for contraception (n = 16) on days 5, 15, and 25 of the menstrual cycle for comparison. The results showed that in women receiving Cyclo-Provera, mean serum E2 concentrations were highest on day 10. The mean E2 peak concentration (95% CI) was 220 (50-372) pg/mL, and approached basal levels by 20 days after Cyclo-Provera injection. In the control group, the mean E2 concentrations (95% CI) were 170 (50-309) pg/mL and 160 (80-250) pg/mL on days 10 and 25 of the menstrual cycle. The data indicate that E2 is absorbed slowly following Cyclo-Provera injection, reaching maximal levels similar to the pre-ovulatory E2 rise by day 10, which then decline to basal levels within 2 to 3 weeks.

Fotherby 1982: A simultaneous pharmacokinetic/pharmacodynamic assessment was undertaken after multiple monthly (28-day) injections of Cyclo-Provera in 11 women (5 White and 6 Hispanic) at 4 centers. Women were studied for one control cycle, three consecutive monthly (28-day) treatment cycles, and two months follow-up. Blood samples were drawn weekly during the three treatment months for analysis of serum MPA and E2 levels. A semilogarithim plot of serum MPA vs time profile after the third monthly injection is shown in Figure 1 and illustrates the high degree of intersubject variability in serum MPA concentrations following IM injection of Cyclo-Provera.

Figure1. MPA Serum Concentration-Time Profile During 30 Days After the Third Monthly Injection of Cyclo-Provera

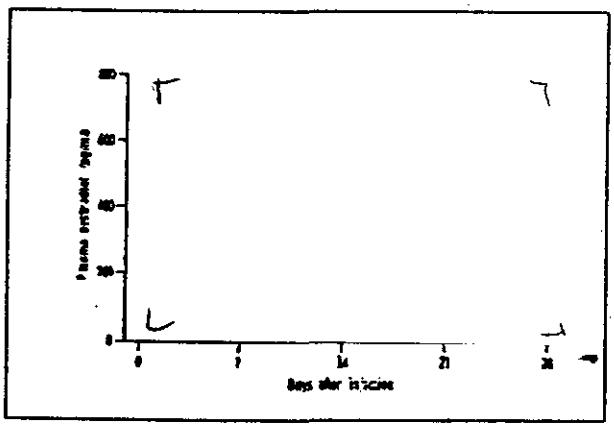


MPA levels were highest (0.70-2.00 ng/mL) during the first 10 days following Cyclo-Provera administration and steadily declined thereafter. The time required for serum MPA concentrations to fall below the detection limit

of the RIA ——— after the third injection of Cyclo-Provera ranged from 28 to 62 days. These results are in agreement with the MPA concentration-time data described in the previous single dose study [Koetsawang 1978], further indicating that prolonged and reproducible serum MPA concentrations are obtained following Cyclo-Provera administration.

Serum E2 concentrations following the third monthly injection of Cyclo-Provera are shown in Figure 2. Serum concentrations of E2 were highest during the first 4 days after Cyclo-Provera injection. Serum E2 peak levels were typically less than 400 pg/mL; only two women had peak concentrations above 400 pg/mL, and both were approximately 600 pg/mL. Serum E2 concentrations were at baseline (typically < 100 pg/mL) by 14 days after Cyclo-Provera administration. A second E2 peak (endogenous E2), reflecting follicular phase activity, was observed in several women during the 4th week after the third injection. These results demonstrate that an exogenous E2 peak similar to the pre-ovulatory surge of E2 that occurs during a normal menstrual cycle is observed within the first 4 days after Cyclo-Provera injection. E2 levels then decline and reach baseline values by day 14.

Figure 2. E2 Serum Concentration-Time Profile During 30 Days After the Third Monthly Injection of Cyclo-Provera



Aedo 1985: A pharmacokinetic and pharmacodynamic assessment of two once-a-month injectable contraceptives (Cyclo-Provera and Mesigyna) was undertaken by Aedo [1985]. Eight white women received Cyclo-Provera every 30 days for three consecutive months. Blood samples were drawn 3 times a week for 90 days following the third (last) injection, and plasma concentrations of E2 and MPA were determined. The mean maximum MPA concentration (95% CI) after the third injection was 1.12 (0.93-1.43) ng/mL. The time (Tmax) to reach peak concentration occurred within the first 10 days postinjection. MPA concentrations were detectable in four women for 30 to 50 days and in the remaining four women for 70 to 90 days after the third injection. In all eight women, MPA levels were measurable at the expected time of the next injection (about 30

days). The mean and 95% CI at this time (just before the next scheduled injection) was 0.28 (0.18-0.43) ng/mL.

Similarly, the mean E2 Cmax (95% CI) was 242.4 (191-308) pg/mL after the third injection of Cyclo-Provera. The mean (95% CI) Tmax was 4 (4-7) days. The E2 peak level after Cyclo-Provera administration was similar to the pre-ovulatory E2 peak concentration. Table 4 summarizes mean peak plasma concentrations of E2 following the third injection. Similar to the previous study [Fotherby 1982], plasma E2 levels decline to basal values (< 100 pg/mL) by day 17 postinjection and are followed by a second E2 peak (endogenous) at about day 49. The results of this study were consistent with other studies showing that the terminal half-life of E2C is much shorter than that of the MPA.

Table 4. Geometric Mean Peak Concentrations (95% CI) of E2 in Plasma Following the Third Consecutive Monthly Injection

Endpoint	Cyclo-Provera		
	n	Level (pg/mL)	Days After Injection
First peak (exogenous)	8	242.4 (190.7-307.8)	4 (4-7)
Level when bleeding started	8	54.5 (40.9-54.5)	17 (15-20)
Second peak (endogenous)	8	414.0 (307.8-552.9)	49 (40-58)
Third peak (pre-ovulatory)	7	256.0 (207.0-326.9)	77 (70-85)

Source: Aedo 1985, Table III, p461 (pmol/L converted to pg/mL)

Sang 1995c and 1996: The extent of drug accumulation following monthly IM injection of Cyclo-Provera was investigated in a longitudinal pharmacokinetic study. Nine Chinese (Asian) women received monthly injections of Cyclo-Provera for 1 year. Blood samples were drawn on days 0, 1, 3, 5, 7, 14, 21, and 28 after the first, sixth, and twelfth consecutive injections for measurement of serum MPA and E2. Pharmacokinetic parameter estimates for MPA and the range of E2 concentrations are shown in Table 5. During the first 6 months of treatment, the MPA Cmax and AUC0-28 increased by 47% and 71%, respectively. No additional accumulation of MPA was noted from the sixth to the twelfth monthly injection. The estimates for mean residence time (MRT) after the first, sixth, and twelfth injections were similar, ranging from 11.98 to 12.77 days. At the end of the first, sixth, or twelfth injection intervals (day 28), serum MPA concentrations (Cd28) ranged from 0.58-0.97 ng/mL. In contrast, serum E2 concentrations were similar after the first, sixth, or twelfth consecutive injections and ranged from 65.9-366.1 pg/mL. There was no apparent accumulation of E2 from

the first through the twelfth injections. Furthermore, peak serum E2 concentrations in the Cyclo-Provera users were within the range of pre-ovulatory rise of E2 in untreated women.

The results of this study indicate that measurable accumulation of MPA was observed after repeated monthly injections of Cyclo-Provera for the first 6 months. However, there was no additional accumulation of MPA from the sixth through the twelfth injections. No accumulation of E2 was observed after 12 monthly injections.

Table 5. Pharmacokinetic parameters of MPA and E2 After the 1st, 6th, and 12th Monthly Injections of Cyclo-Provera

Parameter	Injection Period		
	1st Month	6th Month	12th Month
MPA			
Tmax (day)	3.4 ± 0.9	4.3 ± 2.2	3.7 ± 2.6
Cmax (ng/mL)	1.45 ± 0.49	2.14 ± 0.69	2.15 ± 0.70
AUC0-28day (ng.d/mL)	21.58 ± 10.88	36.90 ± 16.27	37.81 ± 8.44
Mean residence time (day)	11.98 ± 1.08	12.77 ± 0.47	12.43 ± 0.64
E2			
Cmax (pg/mL)	290.2 ± 102.6	366.1 ± 139.9	311.9 ± 146.9
Range during period (pg/mL)	32.2 - 468.1	55.6 - 586.6	34.4 - 616.1

Parameter values are Means ± SD

Source: Sang 1996, p 1-3

3. DOSE PROPORTIONALITY

Throughout the clinical development of Cyclo-Provera, four different dose combinations of MPA:E2C (ie, 50 mg:10 mg, 25 mg:5 mg, 12.5 mg:5 mg, and 12.5 mg:2.5 mg) were investigated in clinical trials. This section summarizes the results of the study [WHO 1987a] that contains dose-proportionality information.

WHO 1987a: The dose proportionality and comparative efficacy of MPA:E2C at two dose levels were investigated in a multicenter, open-label, randomized trial [WHO 1987a]. A total of 44 women were enrolled at three WHO Collaborating Centers for Research in Human Reproduction: Bangkok, Thailand (n = 15); Mexico City, Mexico (n = 16); and, Szeged, Hungary (n = 13). Women were randomly allocated within each center to one of the following treatment groups: 1) Cyclo-Provera (25 mg MPA:5 mg E2C, n = 22) and 2) 12.5 mg MPA:2.5 mg E2C (n = 22). They were studied for one control cycle, three consecutive monthly (28 days) injections, and followed 90 days after the last injection. Serum levels of MPA and E2 were measured three times a week for 90 days following the last (third) injection. Pharmacokinetic data for MPA were available only for the Thailand and Mexico centers.

Serum MPA Concentrations: There were no differences in demographic data among centers or treatment groups except that Hungarian women were almost 10 cm taller than those from Mexico or Thailand [WHO

1987a]. Pharmacokinetic data for MPA are summarized in Table 6 (no MPA data were available from Hungarian women).

Table 6. Pharmacokinetic Parameters of MPA After the Third Monthly Injection of Either 25 mg MPA:5 mg E2C or 12.5 mg MPA:2.5 mg E2C
(Geometric Means and 95% Confidence Intervals)

Center	25 mg MPA:5 mg E2C (n)	Cmax (pg/mL)	Tmax (days)	t½ (days)	12.5 mg MPA:2.5 mg E2C (n)	Cmax (pg/mL)	Tmax (days)	t½ (days)
Thailand	7	3.6 (2.8-4.5)	2.3 (1.8-3.0)	12.1 (10.3-14.2)	8	2.2 (1.8-2.8)	2.4 (1.9-3.0)	14.5 (11.1-18.9)
Mexico	8	1.5 (1.2-1.8)	7.8 (2.0-14.0)	15.4 (11.9-20.3)	8	1.3 (1.1-1.5)	6.3 (2.0-10.0)	11.4 (8.1-21.0)

Source: WHO 1987a

Serum E2 Concentrations: Peak serum E2 concentrations were higher in Thai women by about 4-fold and 3-fold, respectively, as compared with Mexican and Hungarian women. Based on Cmax estimates, serum E2 concentrations increased proportionately with increasing dose in Thai and Hungarian women. Mean E2 Cmax values were higher with the larger dose in Mexican women, but the values were not directly proportional to the dose. Mean Tmax values were similar for all groups. Pharmacokinetic data for E2 are summarized in Table 7.

Table 7. Pharmacokinetic Parameters of E2 After the Third Monthly Injection of Either 25 mg MPA:5 mg E2C or 12.5 mg MPA:2.5 mg E2C
(Geometric Means and 95% Confidence Intervals)

Center	25 mg MPA:5 mg E2C (n)	Cmax (pg/mL)	Tmax (days)	12.5 mg MPA:2.5 mg E2C (n)	Cmax (pg/mL)	Tmax (days)
Thailand	7	736 (568-957)	2 (1-3)	8	303 (208-439)	2 (1-2)
Mexico	8	184 (50-318)	3 (1-8)	8	146 (56-236)	3 (1-5)
Hungary*	7	202 (81-323)	3 (1-6)	6	95 (23-166)	4 (2-7)

Source: WHO 1987a

* Listed incorrectly in the source document (WHO 1987) as Mexico City.

Peak serum E2 concentrations were higher in Thai women by about 4-fold and 3-fold, respectively, as compared with Mexican and Hungarian women.

Overall, serum MPA and E2 concentrations increased with an increase in respective MPA and E2C doses. Peak serum concentrations of MPA and E2 in Thai women were higher than corresponding values in Mexican (MPA and E2) and Hungarian (E2) women, suggesting that both MPA and E2 are absorbed relatively more rapidly in Thai women following Cyclo-Provera administration.

4. SPECIAL POPULATIONS

Formal assessments of the pharmacokinetics of MPA and E2 were not conducted in special populations (eg, geriatric, pediatric, women less than 16 years of age, or women with hepatic and renal diseases).

Race: The pharmacokinetics of MPA and E2C were evaluated in women from different countries (races) in which Cyclo-Provera was investigated. With the exception of Thai (Asian) women, serum MPA and E2 concentrations after Cyclo-Provera administration are similar in women from various countries. Thai women show relatively higher Cmax and shorter Tmax values for both MPA and E2, indicating faster drug absorption following Cyclo-Provera administration [WHO 1987a]. The contraceptive efficacy of Cyclo-Provera was similar in Thai women compared to other populations, indicating that pharmacokinetic differences with regard to contraception are not clinically relevant. However, reversal of the contraceptive effect of Cyclo-Provera is observed earlier in Thai women, consistent with the pharmacokinetic differences observed.

Renal Insufficiency: Cyclo-Provera steroidal components are almost exclusively eliminated by hepatic metabolism. No dose adjustment is necessary in females with renal dysfunction.

Hepatic Insufficiency: Administration of Cyclo-Provera is contraindicated in women with severe hepatic disese. The dosage of Cyclo-Provera has not been established for women with mild or moderate symptomatic liver dysfunction.

5. DRUG INTERACTIONS

Formal assessments for drug-drug interactions involving Cyclo-Provera were not conducted. Also, coadministration of estrogen with MPA does not affect the pharmacokinetic profile of MPA. Similarly, MPA does not affect the pharmacokinetic profile of the coadministred estrogen.

In breast cancer patients receiving high MPA doses (1500 mg/day) as chemotherapy, concomitant administration of aminoglutethamide resulted in lower plasma MPA concentrations [Van Deijk 1985]. However, use of Cyclo-Provera is contraindicated in patients with estrogen-sensitive tumors. Therefore, such interaction would be unlikely with contraceptive use of Cyclo-Provera.

6. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

This section summarizes pharmacokinetic/pharmacodynamic studies that assess the temporal relationship between serum MPA concentrations and suppression of ovulation after repeated monthly dosing, and the return to ovulation after cessation of Cyclo-Provera dosing.

a) ***Serum MPA and Supression of Ovulation (Dose selection for clinical trials):*** The effects of MPA:E2C on suppression of ovulation and on plasma/serum concentrations of the injected steroids were assessed in women of reproductive age after monthly administration at different doses. Three studies [Aedo 1985, Fotherby 1982, WHO 1987a] used 25 mg MPA:5 mg E2C.

The designs of these studies were similar. Women were studied for one control cycle, three consecutive monthly injection cycles, and follow-up (90 days after the last injection). For determination of serum MPA concentrations, blood samples were drawn at various times during the three treatment months [Fotherby 1982], or 3 times weekly for 90 days after the last injection [Aedo 1985, WHO 1987a, WHO Study-A]. For assessment of ovulation, plasma/serum levels of progesterone and E2 were measured weekly throughout the studies; ovulation was defined as plasma/serum progesterone levels > 4.40 ng/mL (> 14 nmol/L) for at least 5 days.

Fotherby 1982: The effects of repeated monthly injections of Cyclo-Provera on suppression of ovulation and on serum concentrations of the administered steroids were investigated in 12 women at four centers: 1) Alexandria, Egypt; 2) Havana, Cuba; 3) Mexico City, Mexico; and 4) Stockholm, Sweden. Woman received IM injections of 25 mg MPA:5 mg E2C at 28-day intervals for 3 consecutive months. Serum MPA concentrations were highest (0.70-2.00 ng/mL) during the first 10 days following Cyclo-Provera administration and steadily declined thereafter. The time required for serum MPA concentrations to fall below the detection limit of the RIA ——— , after the third monthly injection ranged from 28 to 62 days. This concentration-time profile was closely associated with both the magnitude and duration of the pharmacodynamic response observed. Ovulation was suppressed throughout the treatment period, as indicated by serum progesterone levels < 3 ng/mL. No luteal activity was observed during the treatment period. These results suggest that 25 mg MPA:5 mg E2C effectively inhibits ovulation for at least 48 days.

Aedo 1985: The effects of repeated monthly administrations of Cyclo-Provera on ovulation and on plasma MPA concentrations were evaluated in 8 women who received IM injections of 25 mg MPA:5 mg E2C at 30-day intervals for 3 consecutive months. In all 8 women, plasma MPA levels increased during the first 10 days postinjection. The mean maximum MPA concentration (95% CI) after the third monthly injection was 1.12 (0.93-1.43) ng/mL, and Tmax occurred within the first 10 days post injection. MPA levels gradually declined thereafter. MPA levels were detectable in all women up to 50 days, but were lower than the limit of

detection in all but 4 women at 90 days after the third injection. By the end of the injection interval (about day 30), the mean (95% CI) MPA level was 0.28 (0.18-0.43) ng/mL or 0.72 (0.46-1.10) nmol/L.

Progesterone concentration-time profiles during the 90 days following the third monthly injection of Cyclo-Provera were determined. Prior to the first injection, luteal-like plasma progesterone peaks were observed in all 8 women, indicating the presence of normal ovulatory cycles. As expected, plasma progesterone concentrations were completely suppressed after Cyclo-Provera injection in these women. After the third Cyclo-Provera injection, plasma progesterone levels were suppressed for approximately 60 to 70 days post injection. In 3 subjects, limited elevation in progesterone levels occurred within 60-70 days after the third injection. However, this did not reach ovulatory level and was associated with a small elevation in plasma E2 levels. The slow elimination of plasma MPA was associated with progesterone suppression lasting up to 60 days postinjection. These results demonstrate that monthly IM injection of 25 mg MPA:5 mg E2C provides reproducible, prolonged plasma MPA concentrations consistent with suppression of ovulation up to 60 days.

WHO 1987a: The pharmacokinetics and pharmacodynamics of MPA:E2C were investigated at two dose levels. Forty-four (44) women were enrolled from three WHO Collaborating Centers for Research in Human Reproduction: Bangkok, Thailand (n = 15); Mexico City, Mexico (n = 16); and, Szeged, Hungary (n=13). Women were randomly allocated within each center to one of the following treatment groups: 1) 25 mg MPA:5 mg E2C (n = 22) or 2) 12.5 mg MPA:2.5 mg E2C (n = 22). Women were studied for one control cycle, three consecutive monthly (28 days) injections, and two months follow-up.

MPA pharmacokinetic data were available only from the Thailand and Mexico centers. Consistent with previous studies, serum MPA levels increased within the first week after injection of both doses of MPA:E2C, indicating slow systemic absorption from the site of injection. The apparent half-life of MPA ranged from 11.4-15.4 days, and no consistent difference was found among the treatment groups.

The 12.5 mg MPA:2.5 mg E2C dose was found to suppress ovulation in 21 of 22 women. One woman (in the Bangkok center) ovulated during the third treatment period, as indicated by serum progesterone levels of > 4.40 ng/mL (> 14 nmol/L). In contrast, ovulation was completely inhibited for at least 1 month in all 22 women receiving the 25 mg MPA:5 mg E2C dose. There was no noticeable change in the overall efficacy of Cyclo-Provera among women at the three centers. The results of this study support the selection of the 25 mg MPA:5 mg E2C dose in effectively inhibiting ovulation for at least one month after IM administration.

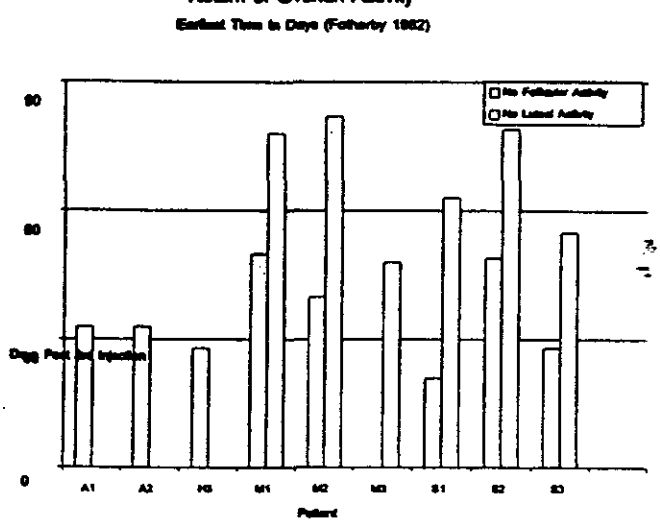
WHO Study-A: To further examine the possibility that a dose lower than 25 mg MPA:5 mg E2C might effectively suppress ovulation, a dose of 12.5 mg MPA:5 mg E2C was evaluated with respect to suppression

of ovulation in 24 women. Consistent with the results of the WHO 1987a study, the 12.5 mg MPA:5 mg E2C regimen failed to consistently suppress ovulation. During the third treatment month, 42% of women receiving 12.5 mg MPA:5 mg E2C ovulated as determined by peripheral progesterone levels persistently > 4.72 ng/mL (> 15 nmol/L).

b) Serum MPA and Return of Ovulation/Menstrual Cycles: To demonstrate that repeated administration of Cyclo-Provera does not permanently suppress the pituitary-ovarian axis leading to infertility, the reversibility of ovulatory suppression was investigated following cessation of both short-term [Aedo 1985, Fotherby 1982, WHO 1987a, WHO Study-A] and long-term [Bassol 1995] Cyclo-Provera therapy. These studies used several indicators for assessment of return to ovulation, including plasma E2 > 150 pg/mL and progesterone > 4.72 to 5.03 ng/mL, and urinary concentrations of estrone glucuronide of 85 to 170 nmol/L, pregnanediol glucuronide of 10 to 22 mol/L and LH of 12 to 75 mUI/mL in at least three consecutive urine samples. Non-ovulatory cycles were indicated by the absence of luteal levels of progesterone following an increase in endogenous E2.

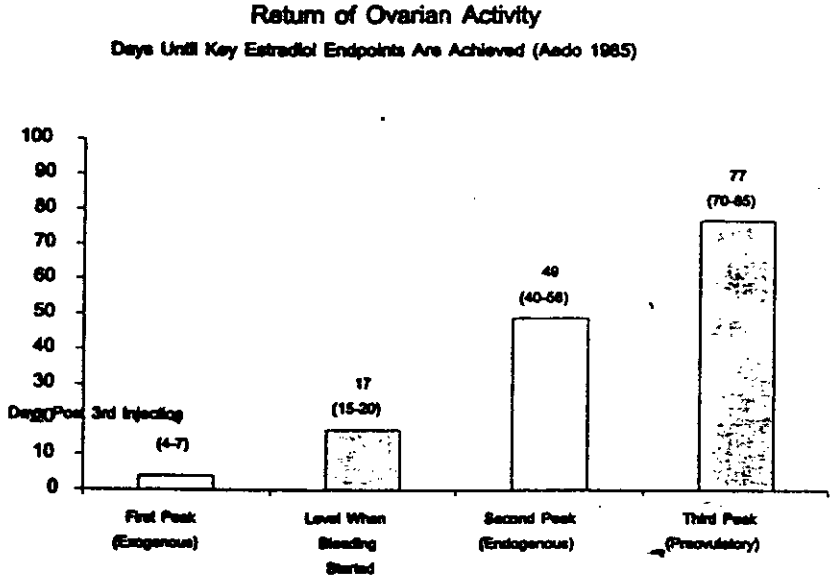
Fotherby 1982: The return of ovarian function (follicular and luteal activities) in 9 women following the third (last) monthly injection of Cyclo-Provera is illustrated in Figure 3. In three women, follicular activity was observed toward the end of the third injection interval indicated by an increase in endogenous E2 levels > 150 pg/mL; however, there was no corpus luteum activity to indicate ovulatory cycles in these women at this time. Follicular activity returned in 8 (73%) of 11 women by 50 days after the last injection. Luteal activity (assessed by plasma progesterone > 3 ng/mL) was not present until at least 48 days after the last injection. By the end of the second and third months of follow-up, 2 (18%) and 6 (54%) of 11 women had ovulated, respectively. Follicular and/or luteal activity information was not provided for several women.

Figure 3. Return of Ovarian Function (Resumption of Follicular and Luteal Phase Activity) in Individual Patients Following the Third Monthly Injection of Cyclo-Provera



Aedo 1985: Return of ovulation was assessed by plasma E2 levels > 150 pg/mL and progesterone levels > 5.03 ng/mL (16 nmol/L) for at least 5 days. Resumption of follicular phase activity following the third injection of Cyclo-Provera is illustrated in Figure 4. In 7 of 8 women treated with 25 mg MPA:5 mg E2C, the first normal preovulatory plasma E2 peak occurred 70 to 85 days after the third injection. Similarly, the first normal ovulatory rise in plasma progesterone levels occurred 71 to 90 days after the third injection. A temporal relationship was apparent between the decline in MPA concentrations following cessation of Cyclo-Provera dosing and the rise in plasma progesterone concentrations. These results demonstrate that suppression of ovulation by Cyclo-Provera is reversible within 2 to 3 months after the last injection of therapy.

Figure 4. Return of Ovarian Function (Resumption of Follicular Phase Activity) Following the Third Injection of Cyclo-Provera



WHO Study 1987a: In this study, ovulation was re-established earliest in women receiving a dose of 12.5 mg MPA:2.5 mg E2C. For both doses of MPA:E2C studied, ovulation returned relatively more rapidly in Thai women compared with Mexican or Hungarian women. These results are consistent with the lower serum MPA and E2 concentrations observed after the administration of the lower dose, and the relatively rapid drug absorption and elimination in Thai women that were found in this study. Table 8. Presents the number of women in each treatment group who ovulated during the third treatment month and in the months post injection

Table 8. Number of Women in Each Treatment Group Who Ovulated During the Third Treatment Month and in The Months Post injection

Treatment MPA:E2C	Center	Number of Subjects	Third Treatment Month	First Month Post-Treatment	Second Month Post-Treatment
25 mg:5 mg	Thailand	7	0	6	7
	Mexico	8	0	4	5
	Hungary	6	0	1	3
	Total	**21**	**0.0%**	**52.4%**	**71.4%**
12.5 mg:2.5 mg	Thailand	8	1	6	7
	Mexico	7	0	5	7
	Hungary	5	0	1	4
	Total	**20**	**5.0%**	**60.0%**	**90.0%**

Source: WHO 1987a.

Bassol 1995: The reversibility of suppression of ovulation after long-term (2 years) treatment was evaluated in 10 women. Ovulation was determined by urinary concentrations of estrone glucuronide (85 nmol/L to 170 nmol/L), pregnanediol glucuronide (10 mol/L to 22 mol/L), and LH hormone (12 mUI/mL to 75 mUI/mL) in at least three consecutive urine samples. Following two years of treatment with 25 mg MPA:5 mg E2C, 6 of 10 women ovulated at least once within 120 days following the last injection. Endometrial bleeding was observed in two women within approximately 4 months after the final injection.

7. POPULATION PK AND PD ANALYSIS

No population PK/PD analysis was performed.

IX. LABELING

The sponsor proposed labeling for Cyclo-Provera is included in Attachment V

REVIEWER COMMENTS:

The following changes are recommended for the Pharmacokinetic subsection of the labeling.

Pharmacokinetics

Absorption:

[redacted]

2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

_____

26 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling