

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708/S-005

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

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20708 (INT)
Compound: Leuprolide Acetate (3.75 and 11.25 mg Lupron Depot®)
Sponsor: Tap Holdings Inc.
Type of Submission: Study Report: Phase 4 PK/PD Study
Date of Submission: April 2, 1998
Reviewer: S.W. Johnny Lau, R.Ph., Ph.D.

Background:

Leuprolide acetate subcutaneous injection (Lupron®) is indicated for the treatment of prostate cancer. Intramuscular injections of (IM) 3.75 mg leuprolide acetate (Lupron Depot®) is indicated for the treatment of endometriosis and anemia associated with leiomyomata. IM 11.25 mg leuprolide acetate (Lupron Depot®) is indicated for the treatment of central precocious puberty. This NDA includes a Phase 4 study to evaluate the comparative pharmacokinetics and pharmacodynamics of IM 3.75 mg Lupron Depot® (every 4 weeks) versus IM 11.25 mg Lupron Depot® (every 12 weeks) for 24 weeks. This study addresses Phase 4 commitments for both NDAs 19943 and 20708 (see Attachment 1). Results of this study will be incorporated into the labeling. Leuprolide is metabolized to an inactive metabolite, M-I, which has a 70% cross-reactivity with leuprolide in . Hence, this study used an method to separate leuprolide and its metabolites before their quantification via

Protocol Number: M96-506 (under IND)

Study Title:

A pharmacokinetic and pharmacodynamic study of Lupron Depot 3.75 mg and 11.25 mg in patients with endometriosis.

Investigators and Locations:

Norman Assad, M.D., Albuquerque, NM, Lawrence Gratkins, M.D., Champaign, IL, William Koltun, M.D., San Diego, CA, Mark Martens, M.D., Minneapolis, MN, Marcia Montgomery, M.D., Nashville, TN, John Pickens, M.D., Memphis, TN, Paul Silva, M.D., La Crosse, WI, Barbara Soltes, M.D., Chicago, IL.

Objectives:

1. compare leuprolide pharmacokinetics between the 2 treatment groups
2. compare serum estradiol concentrations between the 2 treatment groups
3. evaluate the plasma concentrations of M-I to leuprolide with respect to cross-reactivity with former

Study Design:

This was a parallel, 24-week, multicenter, and open-label study. Twenty randomized endometriosis patients (15 completed) received six IM 3.75 mg Lupron Depot® 4 weeks apart. Another 21 such patients received (19 completed) two IM 11.25 mg Lupron Depot® 12 weeks apart. All patients received 500 mg calcium carbonate and 125 mg vitamin D daily as supplement throughout the study.

Drug Administration:

1. 3.75 mg Lupron Depot® Lot No. 14-126-S2; Ampule Lot No. 09-327-AP
2. 11.25 mg Lupron Depot® Lot No. 14-129-S2; Ampule Lot No. 14-180-S2
3. 500 mg calcium carbonate and 125 mg vitamin D (OsCal 500 + D); Lot No. unknown

Blood Sampling and Bioanalytical Analysis:

Blood samples were collected at baseline and every 4 weeks from all patients for the determination of plasma leuprolide and M-I concentrations and serum estradiol concentrations. Plasma leuprolide and M-I concentrations were expressed as plasma leuprolide acetate and M-I (base) concentration, respectively. If Lupron Depot® was administered, blood samples were collected at predose and 4 hours postdose. If Lupron Depot® was not administered, a blood sample was still collected.

Plasma leuprolide concentrations were measured

Recovery: Acceptable.

Linearity: Non-linear.

Accuracy: Satisfactory.

Precision: Acceptable.

Sensitivity:

Plasma M-I concentrations were measured

Recovery: Acceptable.

Linearity: Non-linear.

Accuracy: Satisfactory

Precision: Acceptable.

Sensitivity:

Serum estradiol concentrations were measured

Sensitivity:

Pharmacokinetic and Statistical Analysis:

Predose (trough) plasma leuprolide and M-I concentrations from weeks 4 to 24 were compared between treatment groups via a linear mixed effects model with fixed effects for treatment, week, and treatment•week. Changes from baseline in predose serum estradiol concentrations were compared between treatment groups via ANCOVA with effects for treatment and investigator for each of weeks 4 to 24. Associations between plasma leuprolide or M-I concentrations and changes from baseline in predose serum estradiol concentrations were performed between treatment groups via the Spearman correlation test from weeks 4 to 24.

Results and Conclusion:

Mean (SD) plasma leuprolide and M-I concentrations are in Table I. Mean plasma leuprolide and M-I concentrations versus time plots are in Figures 1 to 4. There was no statistically significant difference in predose plasma leuprolide ($p=0.451$) or M-I ($p=0.290$) concentrations between groups treated with IM 3.75 mg Lupron Depot® every 4 weeks and IM 11.25 mg Lupron Depot® every 12 weeks from weeks 4 to 24.

Mean (SD) serum estradiol concentrations are in Table II. Mean serum estradiol concentrations versus time plots are in Figures 5 and 6. No statistically significant difference was observed between treatment groups for changes of predose serum estradiol concentrations from baselines at any week ($p \geq 0.220$). The mean 4-hour serum estradiol concentrations on week 4 to 20 were consistently slightly higher than the predose serum estradiol concentrations but were still within or near the post-menopausal range.

There was also no statistically significant association between plasma leuprolide or M-I concentrations and changes of serum estradiol concentration from baseline.

Comments NOT to be conveyed to the Sponsor:

1. The bioanalytical assay for leuprolide and M-I in this study appears to be inconsistent with a similar published assay by Ueno and Matsuo (*J. Chromatograph.* 566:57-66 1991; Attachment 2). The recovery of M-I and leuprolide for this study were 67.8-73.7% and 72.4-82.4%, respectively, whereas the recovery of both M-I and leuprolide were $>88\%$ for Ueno's assay. Also, the precision of M-I and leuprolide for this study were 25.1% and 26.6% CV, respectively, whereas the recovery of both M-I and leuprolide were $<5\%$ CV for Ueno's assay.
2. Validation report for the estradiol bioanalytical assay is not provided.
3. No synopsis for regulatory agencies is provided which made it difficult to locate information such as investigator, site, study start and end date, patient accountability, and lot numbers of test medications, etc.)
4. Why were plasma leuprolide concentrations expressed as plasma leuprolide acetate concentrations?

Table I. Plasma leuprolide and M-I concentrations (mean ± SD):

Week	Lupron Depot 3.75 mg/4 Weeks		Lupron Depot 11.25 mg/12 Weeks	
	Leuprolide†	M-I	Leuprolide†	M-I
0-h Plasma Concentration (ng/mL)				
Day 1	0.00±0.00	0.01±0.03	0.03±0.13	0.03±0.11
4	0.06±0.09	0.02±0.05	0.10±0.26	0.05±0.08
8	0.03±0.06	0.02±0.06	0.09±0.18	0.02±0.05
12	0.07±0.08	0.02±0.04	0.05±0.09	0.03±0.07
16	0.06±0.11	0.01±0.03	0.06±0.08	0.04±0.07
20	0.05±0.10	0.03±0.06	0.06±0.08	0.03±0.06
24	0.03±0.08	0.02±0.05	0.04±0.09	0.01±0.03
4-h Plasma Concentration (ng/mL)				
Day 1	9.17±3.39	1.56±0.59	15.90±7.06	2.84±1.90
4	7.69±2.29	1.56±0.54	--	--
8	10.14±5.45	2.04±1.16	--	--
12	7.66±2.44	1.53±0.53	15.98±8.50	2.59±1.46
16	7.94±3.62	1.87±1.27	--	--
20	8.95±3.19	1.50±0.30	--	--

† Expressed as leuprolide acetate.

Table II. Serum estradiol concentrations (mean ± SD):

Week	Lupron Depot	Lupron Depot
	3.75 mg/4 Weeks	11.25 mg/12 Weeks
0-h Serum Estradiol Concentration (ng/dL)		
Day 1	5.8±3.8	6.4±6.0
4	1.6±1.9	1.7±2.2
8	1.8±2.9	1.1±1.0
12	1.6±1.2	1.9±2.4
16	1.4±1.4	1.4±2.2
20	1.6±1.9	1.3±1.9
24	1.2±1.1	1.5±1.8
4-h Serum Estradiol Concentration (ng/dL)		
Day 1	8.2±4.1	9.3±7.6
4	2.5±2.6	--
8	3.0±4.0	--
12	2.2±1.6	2.5±2.9
16	2.3±2.0	--
20	1.9±1.7	--

Figure 1. Mean 0-h Plasma Leuprolide and M-I Concentrations following Intramuscular Injections of Lupron Depot 3.75 mg/4 Weeks

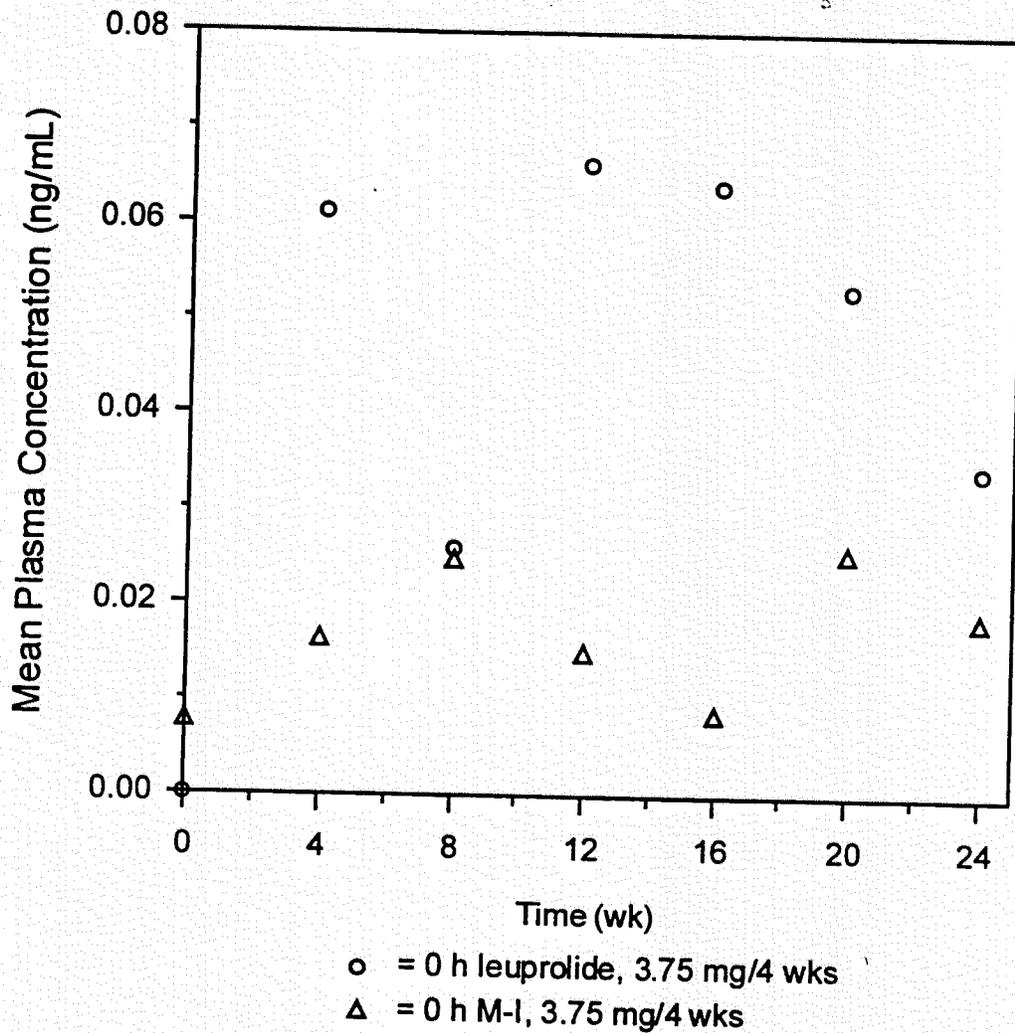


Figure 2. Mean 0-h Plasma Leuprolide and M-I Concentrations following Intramuscular Injections of Lupron Depot 11.25 mg/12 Weeks

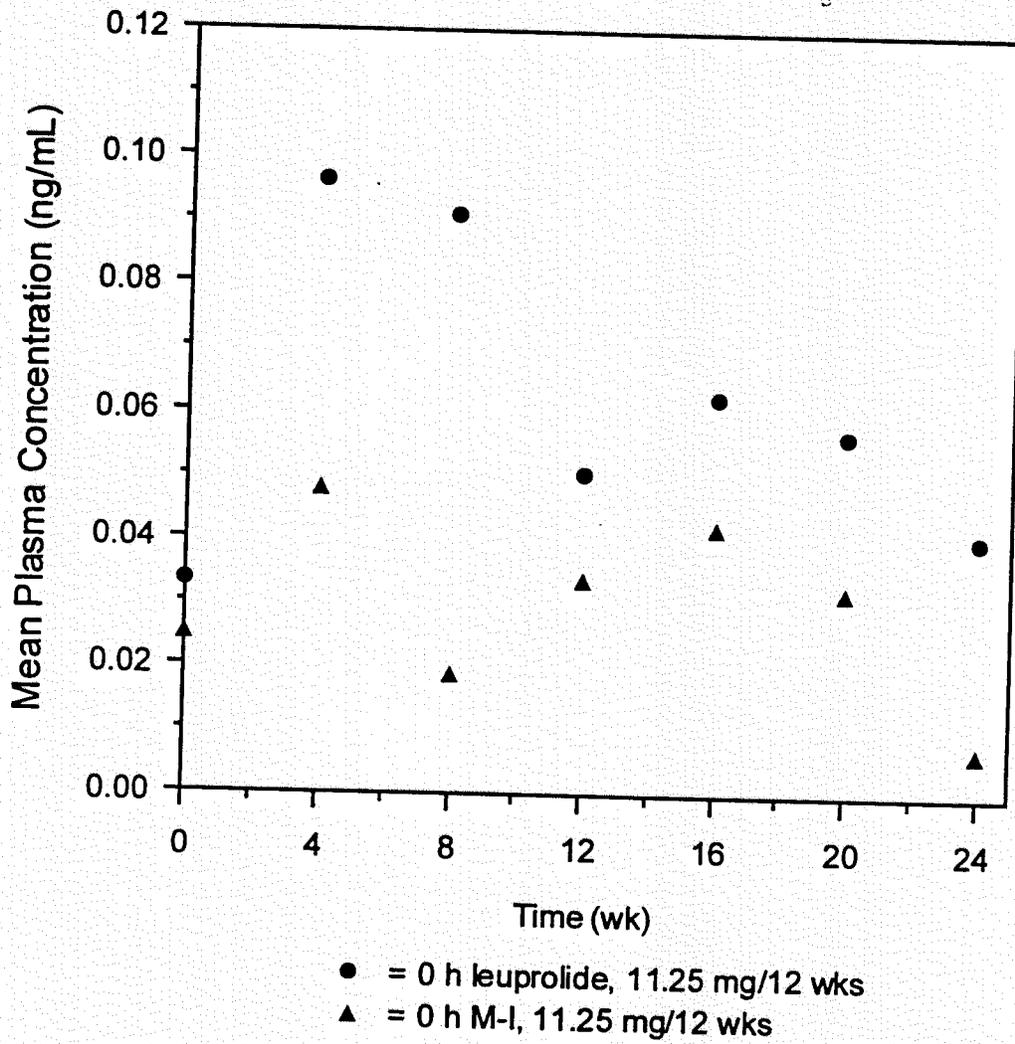


Figure 3. Mean 4-h Plasma Leuprolide and M-I Concentrations following Intramuscular Injections of Lupron Depot 3.75 mg/4 Weeks

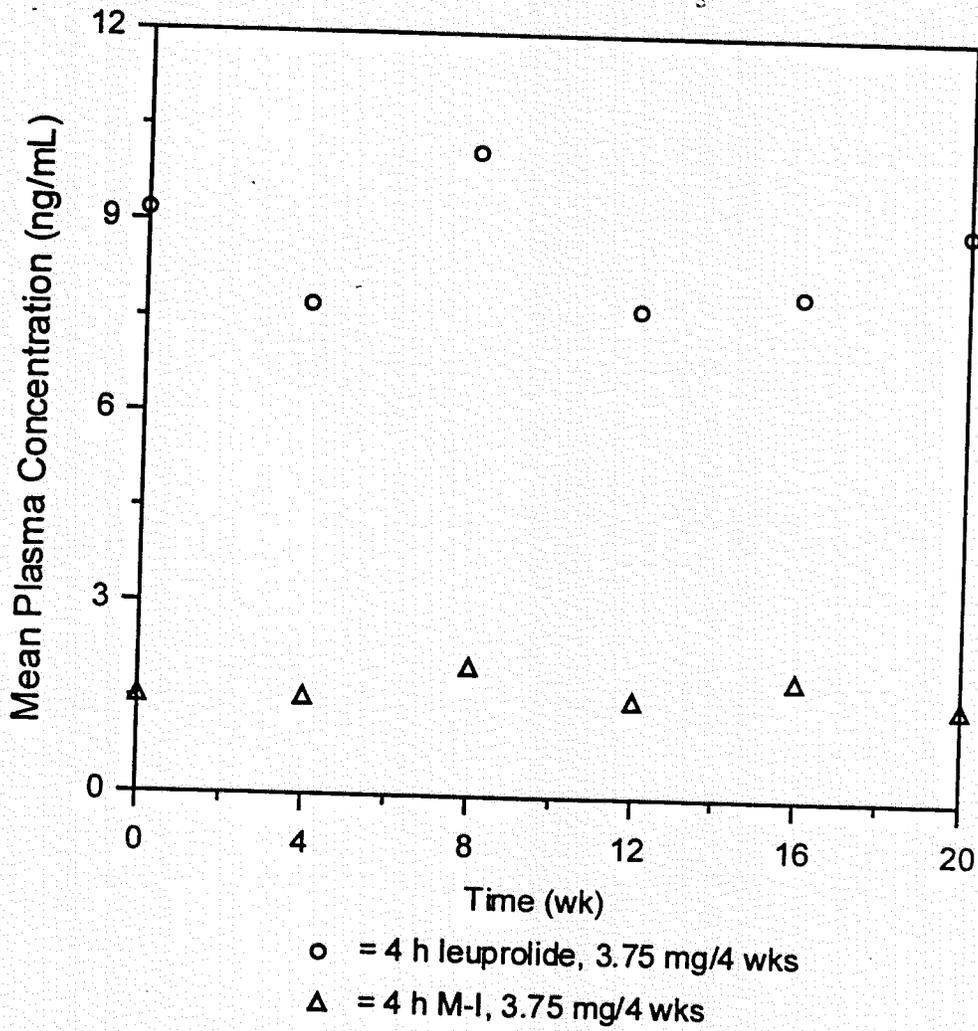


Figure 4. Mean 4-h Plasma Leuprolide and M-I Concentrations following Intramuscular Injections of Lupron Depot 11.25 mg/12 Weeks

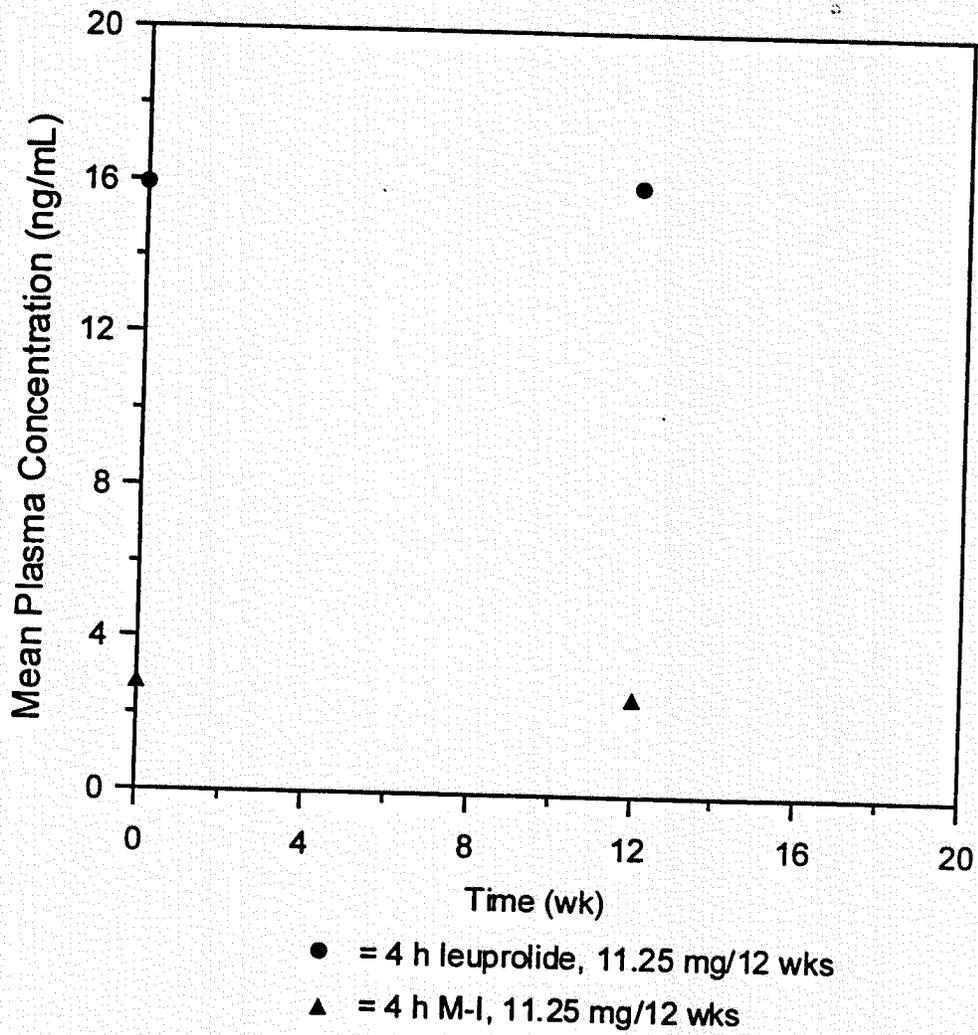


Figure 5. Mean 0-h Serum Estradiol Concentrations

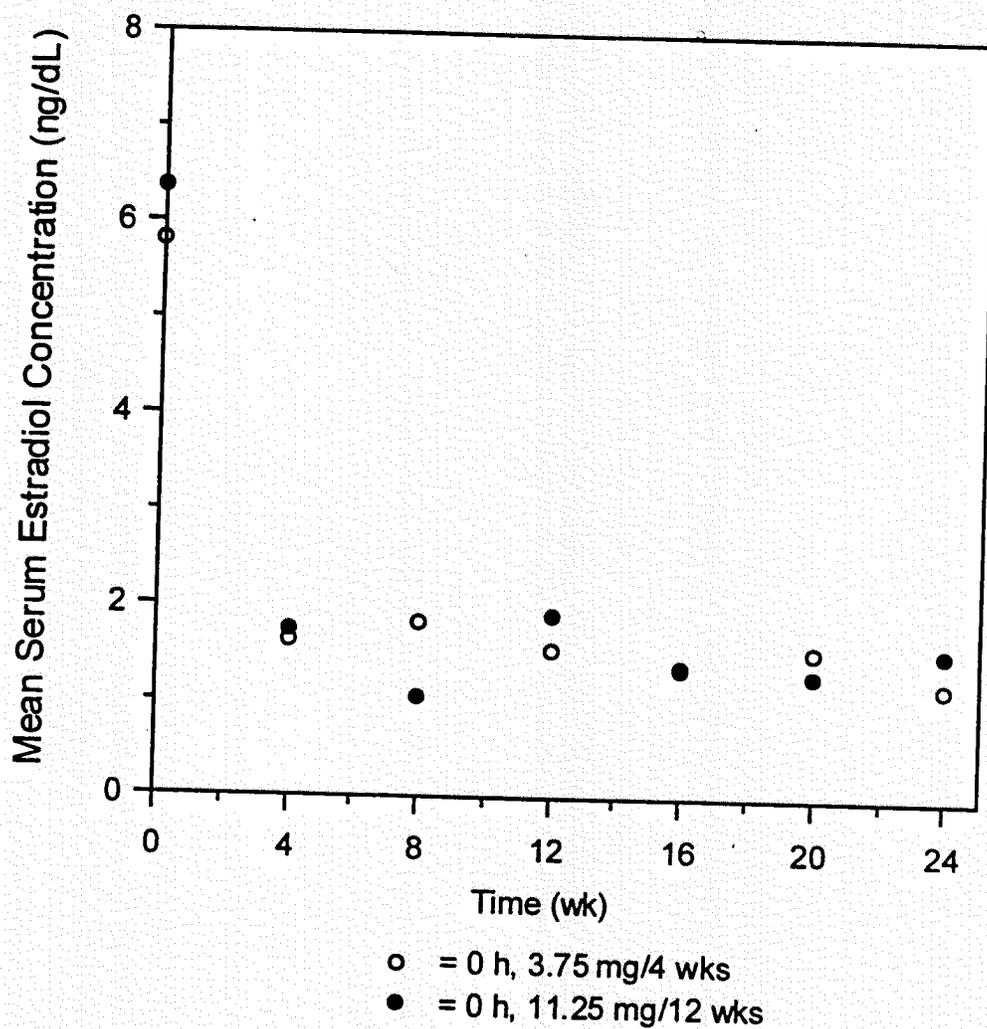
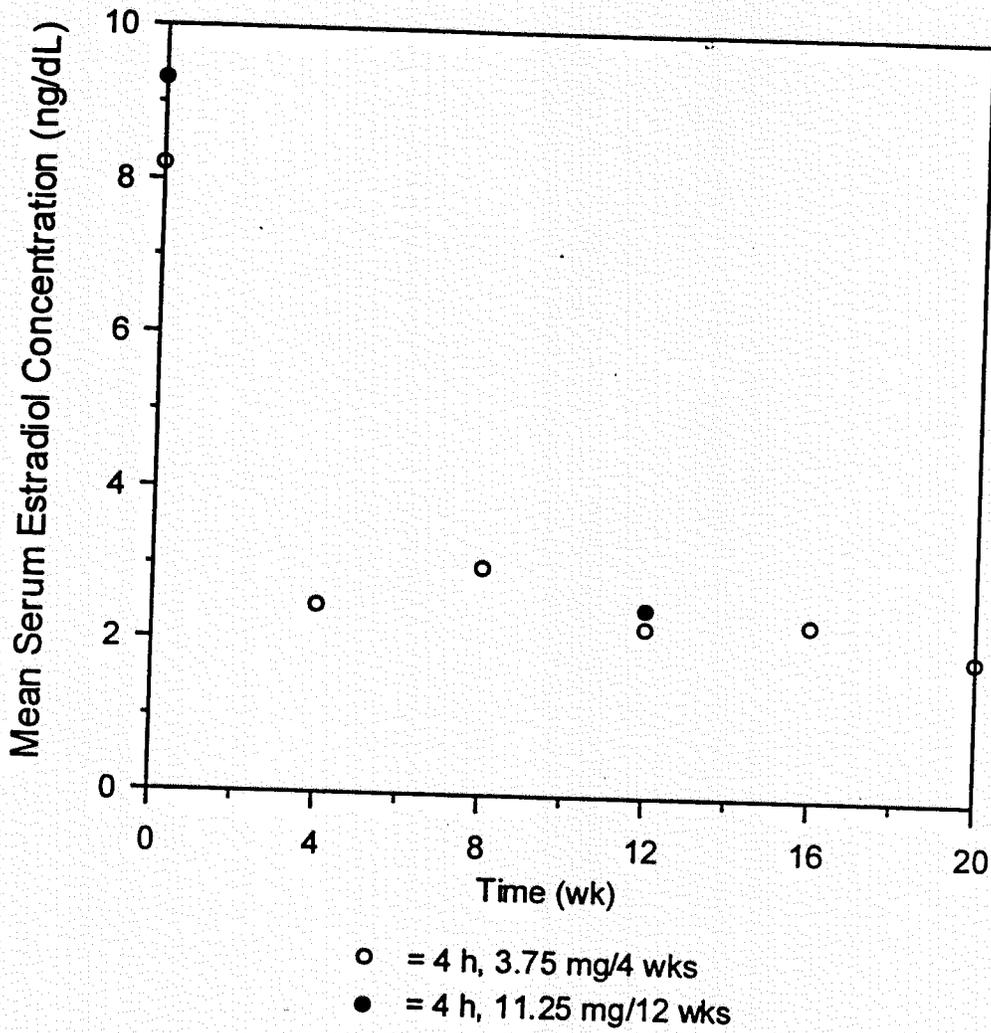


Figure 6. Mean 4-h Serum Estradiol Concentrations



Attachment 1

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CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 19-943

Compound: Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)

Submission Date: 7/18/96 (Amendment Serial No. B-002)

Sponsor: TAP Pharmaceutical Inc.

Type of Submission: Pharmacokinetic/Pharmacodynamic Protocol (Phase IV commitment)

Reviewer: K. Gary Barnette, Ph.D.

Background

NDA 19-943, Lupron Depot® 3.75 mg, for the indication of treatment of leiomyomata uteri (uterine fibroids), was submitted on March 30, 1994 and the biopharmaceutics review was completed on March 1, 1995 by Dr. Hae-Young Ahn, Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). However, only the pharmacokinetics/pharmacodynamics after a single dose of Lupron Depot® 3.75 mg was assessed at that time (Study # M89-37). The recommendation by Dr. Ahn was that an additional, multiple dose (3 monthly doses) pharmacokinetic/pharmacodynamic study in patients with uterine fibroids was needed to completely satisfy the OCPB requirements. A commitment was made by the sponsor on March 22, 1995 to conduct the recommended study, post-approval.

Subsequently, NDA 20-708 Lupron Depot® 11.25 mg (3 month) was submitted on March 6, 1996 for the treatment of both uterine fibroids and endometriosis. A recommendation by the Division of Reproductive and Urologic Drug Products (HFD-580) dated May 20, 1996 (letter included in Attachment 1) proposed a study to satisfy the Phase IV commitment made on March 22, 1995 as well as provide comparative pharmacokinetic and pharmacodynamic data from the currently approved Lupron Depot® 3.75 mg (1 month) and Lupron Depot® 11.25 mg (3 month), currently under review.

The current submission to NDA 19-943 (dated 7/18/96) contains protocol No. M96-506, and follows the study design recommended by the Agency in the May 20, 1996 letter.

Recommendation

It should be noted that Study M96-506 addresses both, the Phase IV commitments for NDA 19-943 and the requirement of comparative pharmacokinetic/pharmacodynamic data for NDA 20-708.

It is stated in the submission that Study No. M96-506 was started by September 15, 1996. Therefore, no further review of this submission is warranted. However, it is recommended that the final study report for Study M96-506 be submitted electronically (WORDPERFECT 6.1 and EXCEL 5.0) as soon as it is available.

The recommendation should be communicated to the sponsor as appropriate.

IS/
K. Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 12/5/96

FT signed by Angelica Dorantes, Ph.D., Team Leader 12/5/96

cc: NDA 19-943, HFD-580 (Fourcroy, Dunston), HFD-870 (M.Chen, Dorantes, Barnette), HFD-870
Clarence Bott (Drug, Chron, Review).