CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-708

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Barnette

JAN 24 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 20-708

Compound: Lupron Depot® 3-month 11.25 mg (leuprolide acetate for depot suspension)

Submission Date: 3/6/96

Sponsor: TAP Holdings Inc.

Type of Submission: Original NDA

Code: 3S

Reviewer: K. Gary Barnette, Ph.D.

I. SYNOPSIS

On March 6, 1996, TAP Pharmaceuticals, Inc. submitted NDA 20-708 to support the approval of Lupron Depot® 3-month 11.25 mg for the management of endometriosis and with iron, for the preoperative hematologic improvement of anemia caused by uterine fibroids. The active drug (leuprolide acetate) used in the to-be-marketed Lupron Depot® 3-month 11.25 mg formulation is the same as that used in the previously approved NDAs 19-010, 19-732, 20-011, 19-943, 20-263 and 20-517. The current formulation is intended to deliver the luteinizing hormone, releasing hormone (LHRH) analogue, leuprolide, continuously for 12 weeks for the suppression of serum estradiol levels.

The current submission contains one pharmacokinetic/pharmacodynamic study (Study # M94-139). This study was designed to establish the single dose pharmacokinetic profile of Lupron Depot® 3-month 11.25 mg and the hormonal response to this formulation of leuprolide. It should be noted that the indicated course of therapy for the management of endometriosis is 6 months of treatment with the Lupron Depot® 3-month 11.25 mg (2 administrations) and up to three months for the preoperative treatment of uterine fibroids.

II. RECOMMENDATION

NDA 20-708 submitted on March 6, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic regulations outlined in 21 CFR 320.

The dissolution method proposed herein is the same as that used in the currently marketed Lupron Depot® 3-month 22.5 mg and is deemed appropriate.

It should be noted that, since the indicated dosage regimen for the preoperative treatment of uterine fibroids is **UP TO** 3-months, use of the Lupron Depot® 3-month 11.25 mg for this indication may generate systemic exposure to leuprolide longer than clinically necessary.

The following labeling comments need to be conveyed as appropriate to the sponsor:

2. The **CLINICAL PHARMACOLOGY** section of the Lupron Depot® 3-month 11.25 mg label should contain the following text;

3. The **PHARMACOKINETICS** section of the label for the Lupron Depot® 3-month 11.25 mg would be as follows;

Additionally, a 6-month, multiple dose pharmacokinetic and pharmacodynamic assessment (Study M96-506) of the Lupron Depot® 3.75 mg to satisfy a Phase IV commitment made on March 30, 1995 for NDA 19-943 was initiated in September 1996. This study includes a pharmacokinetic and pharmacodynamic comparison of the Lupron Depot® 3.75 mg and the Lupron Depot® 3-month 11.25 mg and an assessment of accumulation of leuprolide levels after two administrations of the Lupron Depot® 3-month 11.25 mg. It has been indicated by Dr. Aruna Dabholkar, Associate Director, Regulatory Affairs, TAP Pharmaceuticals that this study will not be completed by the time this review is due. Therefore, since this study will provide additional data for the 3-month depot reviewed herein, it is recommended that the results from this study be submitted as soon as they are available and at that time update the label as appropriate to incorporate these data.

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

RD initialed by Angelica Dorantes,Ph.D., Team Leader AD 1/23/97
FT signed by Angelica Dorantes, Ph.D., Team Leader 1/24/97

cc: **NDA 20-708, HFD-580 (Corfman, Dunson), HFD-870 (M.Chen, Barnette, Hunt, Dorantes), Drug file (Millison, HFD-850).**

TABLE OF CONTENTS:

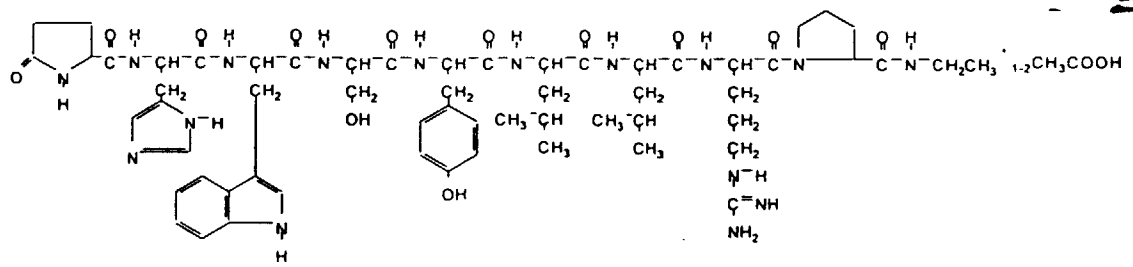
III. BACKGROUND

Leuprolide acetate (Abbott-43818, 5-Oxo-L-prolyl-L-histidyl-L-tryptophanyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate) is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH). Leuprolide acts as a gonadotropin inhibitor and is chemically unrelated to the steroids.

The FDA experience with leuprolide acetate is extensive. Lupron® Injection (daily subcutaneous injection) was approved for the palliative treatment of advanced prostate cancer in April 1985. The objective was to suppress serum testosterone levels to within castrate range without invasive and often debilitating surgery. Subsequently, Lupron Depot® 7.5 mg, designed to provide continuous release of leuprolide over a 4-week (1 month) period, and Lupron Depot® 3-month, 22.5 mg were approved for the same indication in January 1989 and on December 22, 1995, respectively.

Similarly, Lupron Depot® 3.75 mg was approved in October 1990 for the management of endometriosis and in March 1995 for the preoperative treatment of anemia associated with uterine fibroids. The objective for the indications specific for treatment in females is to suppress serum estradiol levels.

The structure of leuprolide acetate is illustrated below.



IV. Formulation and Administration

The formulations pertinent to the approval of the 11.25 mg 3-Month depot of leuprolide are included in Table 1, below. These formulations include the 22.5 mg 3-month depot of leuprolide intended for use in males and the 3.75 mg 1-month depot of leuprolide previously approved for the indications sought in this NDA for the 11.25 mg 3-month depot of leuprolide (endometriosis and uterine fibroids)

Table 1.

Ingredient	11.25 mg 3-month (♀)	22.5 mg 3-month (♂)	3.75 mg 1-month (♀)
Leuprolide Acetate (mg)	11.25	22.5	3.75
Polylactic Acid (mg)	99.3		
D-Mannitol (mg)	19.45		
CMC-Na (mg)			
Polysorbate 80 (mg)			
Water (ml)			

Reviewer Comments:

1. *The 3-month formulations are compositionally proportional with respect to all ingredients except the which is the same. The used in the 3-month depot formulations is necessary to provide the release of leuprolide acetate over the 3 month dosing interval.*

2. *The 1-month depot is compositionally proportional to the 3 month formulations with the notable exceptions of; is structured to provide the release of drug over a 1 month dosing interval.*

V. Analytical Methodology

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Reviewer Comment:

1. *Overall, the assay methodology used appears acceptable.*

2. *Although no cross reactivity with the leuprolide peptide fragments tested was seen, all the possible fragments of leuprolide (metabolites) have not been tested.*

VI. In Vitro Dissolution Testing

The dissolution method proposed for the quality control and release of drug product is as follows;

Apparatus: USP Type II glass (120 ml)
Medium: % polyvinyl alcohol, % polysorbate 80, and mM lactic acid
Procedure:

Specifications:

Time (hours)	Amount Dissolved
	%
	% %
	%

Reviewer Comments:

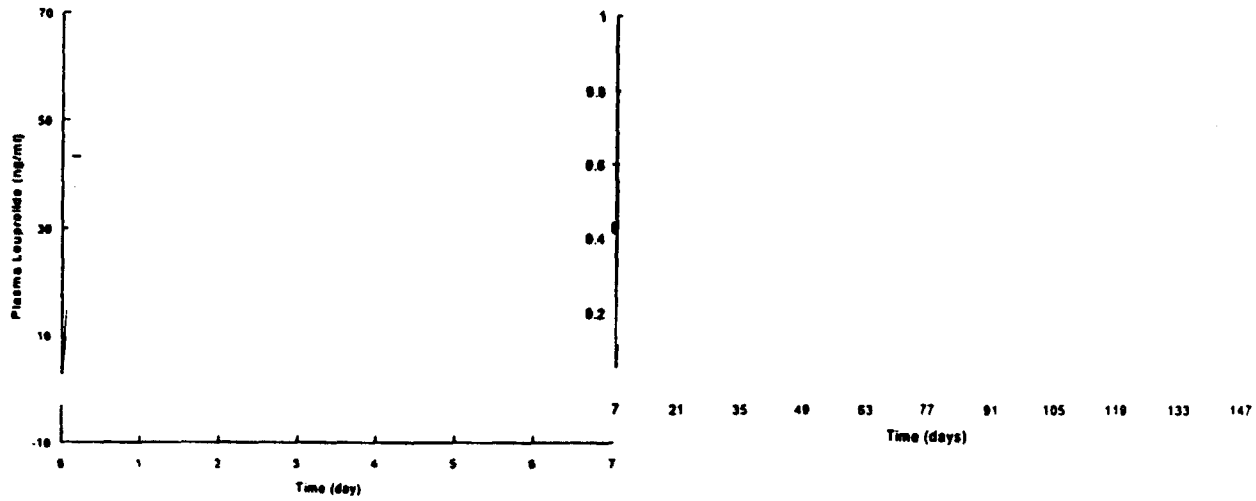
1. *The method and specifications proposed herein are the same as those used for the currently marketed Lupron Depot® 3-month 22.5 mg, indicated for the palliative treatment of advanced prostate cancer.*

2. *The dissolution method and specifications proposed herein appear to be acceptable.*

VII. Pharmacokinetics

Study M94-139 describes the single dose PK of Lupron Depot® 3-month 11.25 mg. Attachment 2 includes the individual study review of Study M94-139. The mean (+ SD) serum leuprolide levels measured in this study are presented in Figure 1.

Figure 1.



The average (± standard deviation) leuprolide concentration (Cavg) and the AUC from Week 3 to Week 12 are as follows;

Cavg (Weeks 3 - 12) 0.23 ± 0.09 ng/ml

AUC (Weeks 3 - 12) 666.7 ± 283.8 ng*h/ml

The mean ± SD leuprolide concentration and the corresponding AUCt for each week (Week 1 through Week 20) are included in Table 7, below.

Table 7. Mean ± SD Leuprolide Acetate Concentrations and AUC

Week	Conc (ng/mL)	AUC (ng•h/mL)	Week	Conc (ng/mL)	AUC (ng•h/mL)
1	0.43 ± 0.17	534 ± 117	11	0.14 ± 0.11	29 ± 19
2	0.50 ± 0.36	79 ± 41	12	0.13 ± 0.10	21 ± 15
3	0.34 ± 0.17	71 ± 38	13	0.09 ± 0.09	19 ± 15
4	0.30 ± 0.15	51 ± 21	14	0.09 ± 0.10	16 ± 17
5	0.27 ± 0.11	44 ± 20	15	0.07 ± 0.09	14 ± 14
6	0.29 ± 0.14	47 ± 22	16	0.08 ± 0.10	15 ± 18
7	0.26 ± 0.14	44 ± 19	17	0.07 ± 0.09	12 ± 12
8	0.24 ± 0.13	43 ± 19	18	0.04 ± 0.07	9 ± 13
9	0.22 ± 0.16	41 ± 23	19	0.02 ± 0.08	5 ± 8
10	0.20 ± 0.13	32 ± 20	20	0.01 ± 0.04	3 ± 7

Reviewer Comments:

1. *The blood sampling times were such that a true evaluation of Cmax, Tmax and AUC∞ are not possible. The most appropriate estimate of systemic exposure of leuprolide is the average concentration of leuprolide from Week 3 to Week 12 (0.23 ± 0.09 ng/mL).*

2. *In a letter to the sponsor dated May 20. 1996 from the Division of Reproductive and Urologic Drug Products (HFD-580) the following protocol was requested. It should be noted that this protocol is also intended to satisfy a Phase IV commitment specified in an approval letter for NDA 19-943. Lupron Depot® 3.75 mg. dated March 20, 1995.*

   Protocol No M96-506

Objectives: *To assess the pharmacokinetics and hormonal response in patients during multiple injections of Lupron Depot 3.75 mg.*
To assess the pharmacodynamic equivalence (suppression and maintenance of suppression of serum estradiol levels) of the Lupron Depot 3.75 mg and Lupron Depot 3-month 11.25 mg.

To assess the PK/PD relationship between plasma leuprolide concentrations and estradiol levels.

Treatment A: *Lupron Depot 3.75 mg x 6 administrations*
Treatment B: *Lupron Depot 3-month 11.25 mg x 2 administrations*

Blood Sampling:

Treatment A: pre-injection and 4-hours post injection at the time of each injection (Days 1, 28, 56, 84, 12, 140 and 168).

Treatment B: pre-injection and 4-hours post injection at the time of each injection (Days 1 and 84) and one sample at Days 28, 56, 112, 140 and 168 after the initial injection.

The sponsor indicated in submission to NDA 19-943 on July 18, 1996 (Amendmen Serial No. B-002) that this study (M96-506) was initiated by September 15, 1996 and is currently being conducted.

3. *It should be noted that the indicated duration of therapy for either of the currently sought indications (treatment of endometriosis and preoperative treatment for uterine fibroids) is 6 months (two administrations of the Lupron Depot® 3-month 11.75 mg). Since no clinically significant accumulation of leuprolide was predicted from the simulation of five administrations of the Lupron Depot® 3-month 22.5 mg (from OCPB/DPE II review of NDA 20-517 by Hae-Young Ahn, Ph.D., dated 12/20/95), accumulation of leuprolide upon multiple administrations of the depot reviewed herein is not predicted and is of little clinical significance.*

A. Metabolism
Since leuprolide is a synthetic nonapeptide analogue of luteinizing hormone releasing hormone (LHRH), its metabolism is similar to endogenous LHRH and consists of catabolization into smaller peptide fragments.

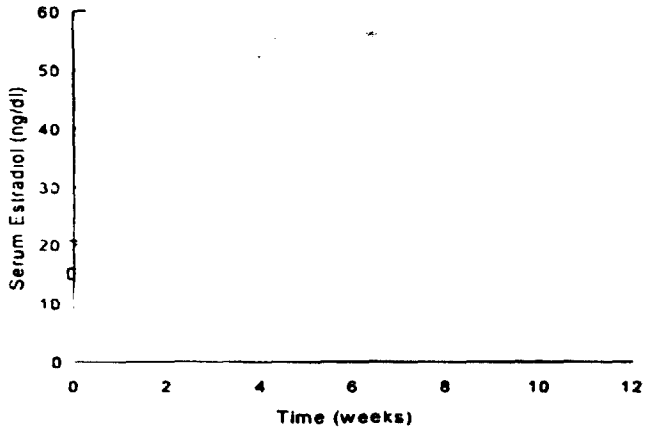
B. Special Populations
The effect of hepatic and renal impairment on the pharmacokinetics/pharmacodynamics of leuprolide has not been determined.

C. Drug Interactions
The potential for pharmacokinetic/pharmacodynamic interaction between leuprolide and other agents has not been assessed, but the likelihood of a clinically significant drug interaction with leuprolide is negligible.

VIII. Pharmacodynamics

The suppression of serum estradiol levels after a single administration of the Lupron Depot® 3-month 11 25 mg are represented in Figure 2.

Figure 2



A between study comparison of estradiol suppression, comparing the currently marketed Lupron Depot® 3.75 mg, 1-month (Studies M86-031 and M90-411) and the Lupron Depot® 3-month 11.25 mg (M94-139) was made by the sponsor, at the request of this reviewer. The results of this comparison are included in Table 8, below.

Table 8.

Time	Treatment	N	Median	Range	Calculated P-value by Statistical Test		
					Savage	Median	Wilcoxon
Day 4	11.25 mg	20	11.50		**0.043**	0.305	0.100
	3.75 mg	60	4.55				
Week 1	11.25 mg	20	2.25		0.200	1.000	0.887
	3.75 mg	72	1.95				
Week 2	11.25 mg	20	0.70		0.127	0.897	0.245
	3.75 mg	84	0.70				
Week 4	11.25 mg	20	0.70		0.298	0.728	0.804
	3.75 mg	99	0.70				
Week 8	11.25 mg	20	0.90		0.942	0.709	0.970
	3.75 mg	94	0.95				
Week 12	11.25 mg	20	0.90		0.520	0.591	0.728
	3.75 mg	93	1.00				

Reviewer Comments:

1. *It appears from these data that the Lupron Depot® 3-month 11.25 mg and the currently marketed Lupron Depot® 1-month 3.75 mg (x 3) are equally effective in the suppression of serum estradiol levels.*

2. *No correlation can be established between serum leuprolide levels (pharmacokinetics) and serum estradiol levels (pharmacodynamics).*

IX. Labeling

The proposed label is included in Attachment 1 (page 11)

Reviewer Comments:

1. Since the Lupron Depot® 3-month 11.25 mg will not be approved for the preoperative hematologic improvement of anemia caused by uterine fibroids, It was stated by Dr. Phil Corfman, Medical Officer (HFD-580)that the proposed combination label containing both the Lupron Depot 3-month 11.25 mg and the Lupron Depot® 3.75 mg would have to be split into two separate labels.

2. The following changes in the **CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS** section(s) of the proposed label are recommended.

- The **CLINICAL PHARMACOLOGY** section of the Lupron Depot® 3-month 11 25 mg should contain the following text:

- The **PHARMACOKINETICS** section of the label for the Lupron Depot® 3-month 11.25 mg should be as follows;

  The *Absorption:* subsection should contain the information specific for the Lupron Depot 3-month 11.25 mg and should contain the following text;

  The *Distribution:*, *Metabolism:*, *Excretion:*, and *Special Populations:* subsections can be identical to that in the currently approved Lupron Depot® 3.75 mg label.

Attachment 2 - Individual Study Summary

M94-139

Study Number: M94-139

Title: Pharmacokinetic and Hormonal Response Study of a Three-Month Depot Formulation of Leuprolide (11.25 mg) in Female Subjects

Objectives: The objectives of this study were to assess the pharmacokinetics of leuprolide 11.25 mg three-month depot formulation in women and to detail the hormonal response with emphasis on length of time for normal endocrine activity to be re-established.

Investigator, Site and Study Dates: Subjects were dosed between November 1994 and February 1995 under the guidance of John H. Cavanaugh, M.D., Ph.D. at the Abbott Clinical Pharmacology Research Unit, Waukegan, IL.

Study Design and Dose Administration: This was an open, single-center study in healthy female volunteers with normal ovarian and menstrual function. The 11.25 mg leuprolide depot formulation was administered intramuscularly on Study Day 0, during the first four days of the menstrual cycle. Blood samples for determination of plasma leuprolide concentrations and hormone levels were to be obtained through Week 20 following the depot injection. The duration and pattern of uterine bleeding (menstrual, intermenstrual, and spotting) were recorded.

Subjects: The study population consisted of 20 healthy female volunteers with normal ovarian function, verified by serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol and progesterone determinations obtained during the mid-luteal phase of the menstrual cycle preceding the Lupron® Depot injection.

Table 9. Patient Demographics

	Age (years)	Weight (kg)	Height (cm)
Mean (range)	33 ± 6 (21-39)	62.6 ± 9.2 (44.5-82.6)	168 ± 7 (154-184)

Clinical Supplies: Leuprolide acetate (11.25 mg) was incorporated into a biodegradable polylactic acid polymer (99.3 mg) and lyophilized with mannitol (19.45 mg), and was supplied as a single lyophilized dose in a vial with a 2 mL diluent solution in an ampule. The diluent ampule contained 10 mg sodium carboxymethylcellulose, 100 mg mannitol, 2 mg polysorbate 80 and water for injection, USP. The lyophilized leuprolide formulation was reconstituted with 1.5 mL diluent immediately before intramuscular injection.

Blood Collection: Blood samples were obtained prior to dosing (0 h) and at 4 h postdosing on Day 0. Single samples were taken on Days 1, 2, 4, and 7 and continued twice a week (at least three days apart) during Weeks 1.5 through 16, and then at the end of Week 17 through Week 20. Blood samples for determination of serum FSH, LH, estradiol, and progesterone concentrations were to be obtained on Day 4, and then weekly at the end of Week 1 through Week 10, twice a week from Week 10.5 through Week 12, and then weekly at the end of Week 13 until normal menstrual activity had resumed and there was presumptive evidence of ovulation based on progesterone levels.

Results:

Pharmacokinetics

Figure 3.

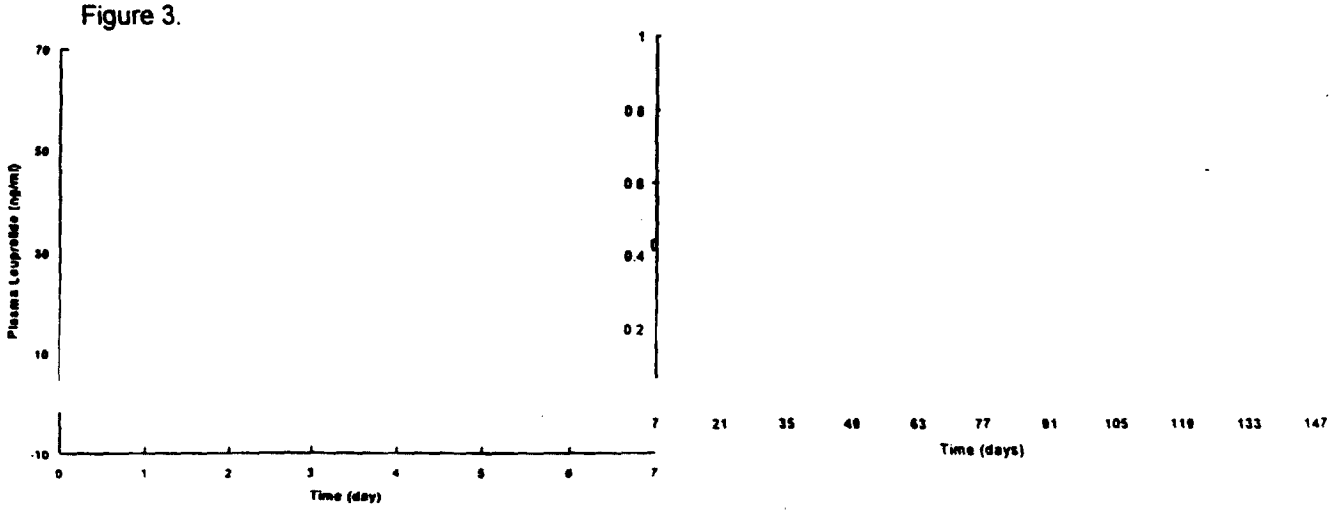


Table 10. Mean ± SD Leuprolide Acetate Concentrations and AUC

Week	Conc (ng/mL)	AUC (ng•h/mL)	Week	Conc (ng/mL)	AUC (ng•h/mL)
1	0.43 ± 0.17	534 ± 117	11	0.14 ± 0.11	29 ± 19
2	0.50 ± 0.36	79 ± 41	12	0.13 ± 0.10	21 ± 15
3	0.34 ± 0.17	71 ± 38	13	0.09 ± 0.09	19 ± 15
4	0.30 ± 0.15	51 ± 21	14	0.09 ± 0.10	16 ± 17
5	0.27 ± 0.11	44 ± 20	15	0.07 ± 0.09	14 ± 14
6	0.29 ± 0.14	47 ± 22	16	0.08 ± 0.10	15 ± 18
7	0.26 ± 0.14	44 ± 19	17	0.07 ± 0.09	12 ± 12
8	0.24 ± 0.13	43 ± 19	18	0.04 ± 0.07	9 ± 13
9	0.22 ± 0.16	41 ± 23	19	0.02 ± 0.08	5 ± 8
10	0.20 ± 0.13	32 ± 20	20	0.01 ± 0.04	3 ± 7

Pharmacodynamics

Figure 4. Serum Estradiol Levels (0-12 weeks)

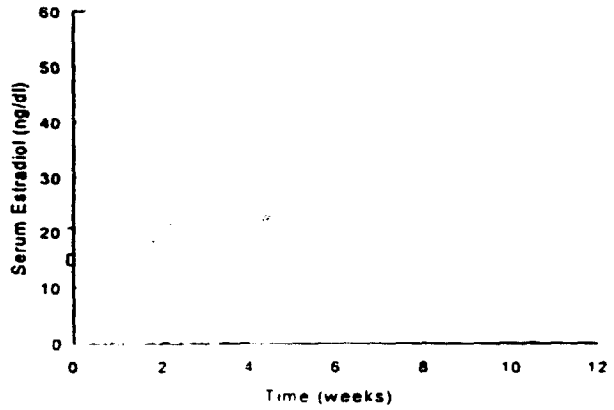


Figure 5. Serum Progesterone Levels (0-12 weeks)

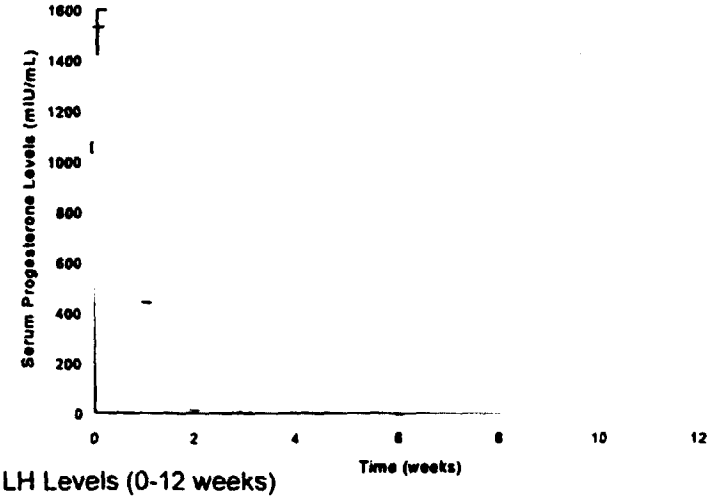


Figure 6 Serum LH Levels (0-12 weeks)

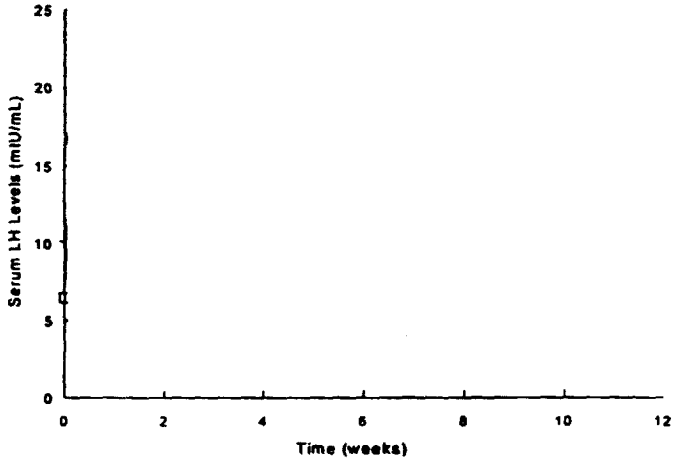


Figure 7 Serum FSH Levels (0-12 weeks)

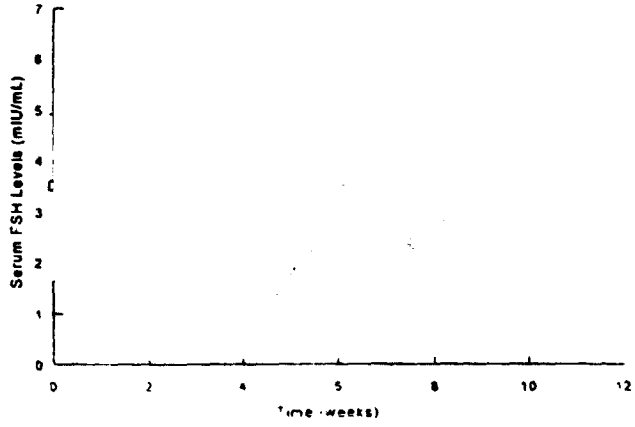


Table 11. Mean ± SD Pharmacodynamic Parameters

Hormonal Response	Baseline	Average Weeks 3-12
LH (mIU/mL)	6.5 ± 3.7	7.3 ± 0.6
FSH (mIU/mL)	3.5 ± 1.4	4.2 ± 1.4
Estradiol (ng/dL)	14.9 ± 5.7	2.0 ± 2.5
Progesterone (ng/dL)	1055 ± 475	22 ± 8

The onset of suppression of estradiol and progesterone ranged for individual subjects between Day 4 and Week 3 after dosing. There were a total of 4 subjects in which serum estradiol levels were >4 ng/dL after suppression at an earlier time point (highlighted in Table 12). However, none of the subjects studied had serum progesterone levels in the ovulatory range (>200 ng/ml) from 3 to 12 weeks after leuprolide administration (see Table 13).

Table 12. Individual Serum Estradiol Level (ng/dL)

Sub #	Pre Dose	Day 4	WEEK												
			1	2	3	4	5	6	7	8	9	10	10.5	11	11.5	12
	29.0	2.8														
	17.0	0.8														
	12.0	1.2														
	13.0	45.0														
	17.0	24.0														
	18.0	15.0														
	13.0	4.7														
	13.0	12.0														
	9.6	45.0														
	17.0	46.0														
	13.0	4.5														
	14.0	1.3														
	25.0	2.1														
	8.6	19.0														
	25.0	13.0														
	10.0	19.0														
	12.0	11.0														
	13.0	2.1														
	9.1	32.0														
	8.9	6.3														

Table 13. Individual Serum Progesterone Level (ng/dL)

Sub #	Pre Dose	Day 4	WEEK												
			1	2	3	4	5	6	7	8	9	10	10.5	11	11.5	12
	1553.0	63.0														
	461.0	42.0														
	1392.0	29.0														
	1443.0	259.0														
	1474.0	62.0														
	1270.0	135.0														
	950.0	177.0														
	958.0	82.0														
	420.0	232.0														
	893.0	340.0														
	796.0	71.0														
	2390.0	27.0														
	1004.0	57.0														
	228.0	111.1														
	827.0	19.0														
	1332.0	69.0														
	815.0	697.0														
	1036.0	25.0														
	910.0	325.0														
	950.0	103.0														

Three out of the 20 subjects studied herein experienced menses after initiation of therapy. A review of the demographics of these three subjects did not yield any significant differences. The dates of the menses and the serum estradiol and progesterone levels prior to the menstrual period are included in Tables 14 and 15.

Table 14

Subject #	Day 1 of bleeding (duration of menses)	Serum Estradiol Levels (ng/dl)				
		Day 0	Day 4	Day 7	Day 14	Day 21
	7 (12)					
	23 (5)					
	16 (4)					
Mean ± SD (all subjects)		14.9 ± 5.7	15.3 ± 15.5	18.8 ± 26.5	14.4 ± 39.0	0.8 ± 0.5

Table 15

Subject #	Day 1 of bleeding (duration of menses)	Serum Progesterone Levels (ng/dL)				
		Day 0	Day 4	Day 7	Day 14	Day 21
	7 (12)					
	23 (5)					
	16 (4)					
Mean ± SD (all subjects)		1055.1 ± 475.2	146.3 ± 163.0	116.8 ± 323.1	36.1 ± 32.8	23.2 ± 10.1

Normal menstrual activity after suppression resumed in a median of 168 days after dosing (24.1 weeks), ranging between days (weeks). Estradiol levels returned to normal levels at a median of 21 weeks after dosing, and the time after dosing for progesterone to return to a concentration in the ovulatory range (>200 ng/dL) had a median value of 23 weeks, with individual values ranging from weeks. There was a significant correlation between the time after dosing for progesterone to return to a concentration of 200 ng/dL or greater (ovulatory range) and the day of return of menses (r^2=0.85).

Conclusions:

1. Following the initial burst of leuprolide from the formulation, which is characteristic of this type of preparation, the Lupron Depot® 3-month 11.25 mg formulation provided a relatively constant release rate of the drug during the intended 12-week treatment duration.

2. Leuprolide concentrations were sufficient in most patients to suppress estradiol and progesterone levels and menses throughout the 12-week treatment period.

3. No direct relationship could be observed between leuprolide concentrations and hormonal response or menstrual activity; that is, higher concentrations were not related to greater suppression.

Reviewer Comments:

1. The blood sampling schedule during the first 2 days after administration was such that a proper assessment of Cmax and AUC was not possible. Therefore, the average leuprolide concentrations from weeks 3 to 12 are the most appropriate assessment of systemic exposure of leuprolide from Lupron Depot® 3-month 11.25 mg.

2. As is the case with other, currently marketed leuprolide formulations, a relationship between plasma leuprolide concentrations and estradiol suppression was not observed.