XI. Attachment 1: Proposed Labeling

APPEARS THIS WAY
ON ORIGINAL

22 pages redacted from this section of the approval package consisted of draft labeling

APR 2 8 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 20-715

Compound: Decapeptyl™ (3.75 mg triptorelin pamoate for depot suspension) Depot

Submission Date: 6/24/96
9/6/96 (Serial No. BB)
10/15/96 (Serial No. BB)

Sponsor: Debio Recherche Pharmaceutique SA

Type of Submission: Original NDA (NME)

Code: 1S

Reviewer: K. Gary Barnette, Ph.D.

I. SYNOPSIS

NDA 20-715 for Decapeptyl™ (3.75 mg triptorelin pamoate for depot suspension), was submitted by Debio Recherche Pharmaceutique SA on June 24, 1996. Triptorelin pamoate is a new molecular entity and is a synthetic decapeptide analog of naturally occurring luteinizing hormone releasing hormone (LHRH) that acts as a potent inhibitor of gonadotropin secretion. The depot formulation reviewed herein is intended to release triptorelin for a 28 day dosing interval. The indication sought is the palliative treatment of advanced prostate cancer.

The submission to NDA 20-715 contained 7 single dose pharmacokinetic studies in humans. These studies included 2 pivotal bioequivalence studies (using the to-be-marketed formulation), 2 supportive bioequivalence studies (not using the to-be-marketed formulation), an absolute bioavailability study, a pharmacokinetic study in renal and hepatic impaired patients and a comparative pharmacokinetic study between radiolabeled triptorelin and endogenous GnRH.

In vitro dissolution data, protein binding (albumin) and assay validation information were also included and reviewed herein.

Additional information concerning the anatomical site of injection in the pivotal clinical and pharmacokinetic trials and *in vitro* dissolution testing was submitted on September 6, 1996 (Serial No. BB) and additional pharmacokinetic information was submitted on October 15, 1996 (Serial No. BB).

II. RECOMMENDATION

NDA 20-715 submitted on June 24, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). The following deficiencies in the application were found;

1. The proposed to-be-marketed formulation is not bioequivalent to the formulations used in the pivotal clinical trials. The sponsor maintains that pharmacodynamic equivalence (maintenance and suppression of serum testosterone levels) exists. However, only single dose studies comparing the pharmacodynamics of the to-be-marketed formulation and that of the clinically tested formulations have been conducted. The difference in the triptorelin concentration versus time profiles of the relevant formulations may be clinically significant, due to spike levels of triptorelin that occur within 3 hours of dosing of the to-be-marketed formulation that may more readily induce a secondary flare (acute-on-chronic) of testosterone levels resulting in escapes from castrate levels than the clinically tested formulations which do not result in a spike level of triptorelin.

2. The proposed dissolution testing method is NOT acceptable. The proposed paddle speed (200 rpm) may result in shearing or breaking of the microgranules rather than dissolution.

It is recommended that the sponsor use acidic media including a surfactant (if necessary), variable media temperature and the paddle speed not exceeding [redacted] rpm. If a solubility problem persists, the sponsor should consider the addition of alcohol to the medium.

The sponsor should submit complete individual and mean dissolution profiles (numerical and graphical) from at least 12 units of the clinical lot(s) and from a full scale batch of the proposed to-be-marketed product to the agency for review. Samples should be collected every 1-4 hours until complete dissolution is achieved of a plateau is reached. Dissolution specifications for a minimum of three points (four are preferable) should be proposed; ideally the last point should be set at [redacted]% of drug dissolved. The proposed ranges should be based on mean ± 10% of the bio/clinical lot(s) dissolution data.

Due to the lack of bioequivalence between the to-be-marketed formulation and the clinically tested formulation and the possible clinical implications, OCPB/DPE II is of the opinion that the sponsor has NOT provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic regulations.

Comments 1 and 2 and the Recommendation should be communicated to the sponsor, as appropriate. Further clarification of the comments can be obtained by contacting the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II.

/S/

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 4/14/97
FT signed by John Hunt, Deputy Division Director /S/ 4/97

cc: **NDA 20-715, HFD-580 (Shames, Dunson), HFD-870 (M.Chen 13B-17, Dorantes, Barnette), HFD-340 (Viswanathan), Drug file (CDR, Barbara Murphy).**

TABLE OF CONTENTS:

III. Background

Pharmacologically, luteinizing hormone releasing hormone (LHRH), also known as gonadotropin releasing hormone (GnRH) stimulates the gonadotroph cells to synthesize and release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins stimulate the gonadal production of sex steroid hormones and gametogenesis. Continuous exposure of the gonadotroph cells to LHRH or LHRH analogs causes the desensitization of gonadotropin secretion and gonadal suppression, resulting in a marked decrease in testosterone production. Chronic exposure to LHRH analogs induces chemical castration in man. Therefore, since prostate cancer is androgen dependent and the gold standard for the palliative treatment of advanced prostate cancer is surgical castration, medical (chemical) castration is effective alternative treatment.

Triptorelin, the active ingredient in Decapeptyl™, is a synthetic decapeptide LHRH analog/agonist. The structure of triptorelin includes 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-**D-tryptophyl**-L-leucyl-L-arginyl-L-proglycine and differs from endogenous LHRH only in the sixth position (D-Trp), which contains a L-glycine. Currently the Agency has approved two LHRH analogs for the palliative treatment of advanced prostate cancer, Lupron® (leuprolide acetate) and Zoladex® (goserelin acetate). Similarly, the approved LHRH agonists differ from endogenous LHRH and each other only in the D-amino substitution at the sixth position. Therefore, although Decapeptyl™ is a new molecular entity, the Agency has significant experience in the use of this drug class for the indication sought herein.

Additionally, Decapeptyl™ has an extensive foreign marketing history and Table 1 includes the countries in which Decapeptyl™ has been approved and dates of approval for the treatment of prostate cancer.

Table 1

Licensee	Country	Approval Date	Licensee	Country	Approval Date	Licensee	Country	Approval Date
IPSEN BIOTECH	Bahrain	2/94	FERRING	Austria	3/94	TECNO-FARMA	Bolivia	12/93
	Belarus	4/95		Bulgaria	11/91		Chile	5/95
	Belgium	10/88, 7/92		Denmark	1/93		Ecuador	1/94
	Congo	8/93		Finland	9/91		Mexico	7/94
	El Salvador	2/94		Germany	2/86		Paraguay	7/93
	France	3/86, 5/91		Hong Kong	6/90		Peru	5/94
	Gabon	1/93		Hungary	6/91			
	Greece	9/94, 11/91		India	7/93			
	Guatemala	6/94		Israel	3/86			
	Ireland	12/89, 1/92		Kuwait	1/95	ACHE	Brazil	3/90
	Italy	1/90, 12/91		Malaysia	3/92			
	Kazakhstan	5/95		Netherlands	1/91			
	Lebanon	7/93		New Zealand	4/90			
	Luxemburg	1/88, 6/91		Pakistan	9/94			
	Madagascar	9/92		Saudi Arabia	7/90			
	Mauritius	10/94		Singapore	11/90			
	Morocco	3/91, ???		Slovakia	11/87			
	Panama	5/94		South Korea	1/90			
	Portugal	1/92, 4/93		Soviet Union	6/89	SIDUS	Argentina	6/89, 2/94
	Romania	7/93		Sweden	10/86			
	South Africa	5/89, 7/94		Switzerland	12/93			
	Spain	4/90, 10/91		Taiwan	12/92			
	Tunisia	9/93		Thailand	12/92			
	UK	12/94		Turkey	???			
	UAE	4/93						
	Vietnam	7/94						
	Ukraine	6/95						

IV. Administration

The anatomical site of administration used in the human pharmacokinetic and bioavailability studies (DEB-95-TRI-02, DEB-93-TRI-05, R.92.10.98 and 017-001) and the pivotal clinical trials is the upper outer quadrant

of the buttock. In studies where multiple dosing was conducted, injections were alternated on the right or left side.

V. Formulation

The formulations of Decapeptyl™ used in the clinical and pharmacokinetic studies reviewed herein are included in Table 2. It should be noted that Formulation F is the proposed to-be-marketed formulation of Decapeptyl™.

Table 2.

Ingredient	Formulation A	Formulation C	Formulation D	Formulation E	Formulation F
Dosage Form	Acetate	Acetate Microspheres	Lyophilized Acetate Microspheres	Pamoate Microgranules	Lyophilized Pamoate Microgranules
Triptorelin		3.75 mg	3.75 mg	3.75 mg	3.75 mg
50:50 Poly (d,l-lactide-co-glycolide)					170 mg
Mannitol, USP		85 mg	85 mg		85 mg
Carboxymethylcellulose sodium, USP			30 mg		30 mg
Polysorbate 80, USP					2 mg
Methylene Chloride					
0.9% NaCl	qsad				
Sterile Water for Irrigation, USP		2 ml	2 ml	2 ml	2 ml
Pharmacokinetic Studies	DEB-95-TRI-03 Iven's Opinion	Iven's Opinion DEB-95-TRI-02 O17-001 R92.10.98	DEB-93-TRI-05 R92.10.98	017-001	DEB-95-TRI-02 DEB-93-TRI-05
Pivotal Clinical Studies	914CL14P	914CL14P 914CL17E 914CL7P	52014 ST 8040		

Reviewer Comments:

1. *The proposed to-be-marketed formulation (Formulation F) was not used in any of the pivotal clinical trials.*

2. *The to-be-marketed formulation has not been used in any of the countries where Decapeptyl™ has been approved for the palliative treatment of advanced prostate cancer.*

3. *The sponsor seeks the approval of Formulation F (lyophilized triptorelin pamoate), rather than one of the triptorelin acetate formulations used in the clinical studies, because the acetate formulations require the use of [redacted] in manufacturing and [redacted] during their shelf-life, while Formulation F does not.*

VI. Analytical Methodology

The serum triptorelin concentrations were estimated by a [redacted] radioimmunoassay, using direct [redacted] human samples. Serum testosterone levels were estimated with a radioimmunoassay with a rabbit capture antibody. The validation for the testosterone RIAs used in the pivotal bioequivalence studies, DEB-95-TRI-02 and DEB-93-TRI-05 and an additional bioequivalence study R92.10.98. The validation data from the triptorelin and testosterone radioimmunoassays used in the studies

reviewed herein are included in Table 3.

Table 3

	Triptorelin	Testosterone
Sensitivity	— ng/ml	— nmol/L
Accuracy (recovery)	— %	
Intra-assay CV %	— %	%
Inter-assay CV %	— %	%
Specificity	endo. GnRH % LH % FSH % somastatin % TRH %	— % — % — %

Reviewer Comment: *The assay methodologies used for the determination of triptorelin and testosterone are acceptable.*

VII. *In Vitro* Dissolution Testing

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

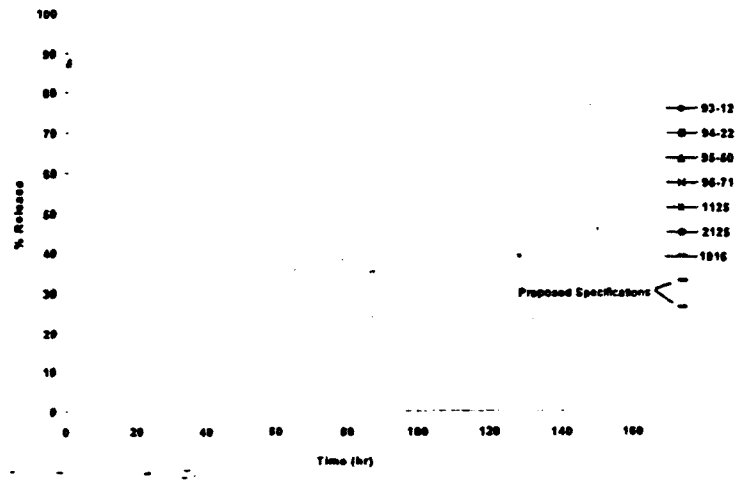
Apparatus: USP Type II (500 ml)
Medium: water:methanol (95:5)
Procedure:

Specifications:

Time (hours)	% Label Claim
hr ± min	% - %
hr ± min	% - %
hr ± min	% - %

The dissolution profiles for various lots of the proposed to-be-marketed formulation as determined by the sponsor *in vitro* dissolution testing method are illustrated in Figure 1.

Figure 1.



In a letter from the Division of Reproductive and Urologic Drug Products (HFD-580) dated August 23, 1996 the following *in vitro* dissolution information was requested. The sponsor's responses are in italic.

1. Please submit dissolution data/profile and particle sizes of biolot No. DLGSD-93-08 that was used in bioequivalence study DEB-93-TRI-05.

Lot DLGSD-93-08 was released prior to development of the [redacted] dissolution test proposed for current product release testing. However, the [redacted] dissolution test and the test for particle size were performed as part of release testing. Results of release testing for lot DLGSD-93-08 showed [redacted] % of peptide released at [redacted]r and [redacted] % of microgranules sized <100 µm.

2. To support the use of hydroalcoholic medium, water:methanol (95:5), and a selected paddle speed of 200 rpm, please provide the following information:

a. The pH solubility profile of triptorelin;

Triptorelin pamoate was poorly soluble [redacted] in aqueous buffer at both pH 4.5 (0.05M acetate buffer) and pH 7.4 (0.05M phosphate buffer). The pH solubility profile of triptorelin pamoate was not determined beyond the physiological range.

b. Dissolution data using non-organic solvent(s), including sink condition information at 37°C for various aqueous media;

Dissolution test development studies for triptorelin pamoate microgranules explored both aqueous and organic dissolution media, all using the same test method. Dissolution media tester included:

- *3.5 mM phosphate buffer, pH 7.4*
- *5 mM citric acid/10 mM phosphate buffer, pH 5.0*
- *10 mM acetate buffer, pH 5.0*
- *0.05M phosphate buffer, pH 7.40 (USP buffer)*
- *0.05M acetate buffer, pH 4.50 (USP buffer)*
- *Water*

Additives to these dissolution media included [redacted]

In general, aqueous media presented problems with inadequate peptide solubility [redacted] leading to poor sink conditions and poor peptide stability [redacted] and the addition of preservatives [redacted], antioxidants [redacted] and detergents [redacted] accelerated peptide degradation, with most dissolutions showing insufficient release leading to a low and constant [redacted] %) peptide concentration in the dissolution medium over 6 to 7 days.

c The rationale of selecting the above hydroalcoholic solvent as a medium.

The water/methanol dissolution media was selected based on three factors:

- *The test should be performed in sink conditions (i.e. maximum concentration at [redacted]% of solubility in medium) to ensure that dissolution, rather than simply peptide solubility, is being measured;*
- *The peptide should not show significant degradation in the medium over the period of testing; and*
- *The test should reflect both an "initial burst" effect and a long-term release, to mimic the release of peptide from microgranules in vivo.*

Only the water/methanol system satisfied all three criteria.

Reviewer Comments:

1. *The proposed dissolution testing method is NOT acceptable. The proposed paddle speed (200 rpm) may result in shearing or breaking of the microgranules rather than dissolution. It is recommended that the sponsor use an acidic media including a surfactant and variable temperature. The paddle speed should not exceed [redacted] rpm. If a solubility problem persists, the sponsor should consider the addition of alcohol to the medium.*

2. *The lots of Decapeptyl™ that were used to establish the dissolution release specifications were NOT used in the clinical or pharmacokinetic studies.*

3. *Batches 93-12, 94-22 and 95-50 fail to fall within the proposed release specifications.*

4. *Since the cumulative % of label claim dissolved is used (%release), it is unclear why batch 94-22 has [redacted]% at [redacted] hours, [redacted]% at [redacted] hours, and rises again to [redacted]% at [redacted] hours.*

VIII. Pharmacokinetics

A summary of the pharmacokinetic studies submitted to support the approval of Decapeptyl™ is included in Table 4 and a detailed description of these studies is included in Attachment 2 (page 23).

Table 4. Study Summary

	Study Design	Dosing	Subjects	Pg #
DEB-95-TRI-02	BIOEQUIVALENCE: single dose, crossover	3.75 mg IM, clinically tested formulation (C) 3.75 mg IM, to-be-marketed formulation (F)	24 healthy ♂	24
ORG 017-001	BIOEQUIVALENCE: Two-way, Randomized, Double-blind, Crossover	3.75 mg IM, q28dx2 clinically tested formulation (C) 3.75 mg IM, q28dx2 Formulation E	30 prostate cancer patients	27
DEB-93-TRI-05	BIOEQUIVALENCE: Single Dose, Randomized, Crossover	3.75 mg IM, clinically tested formulation (D) 3.75 mg IM, to-be-marketed formulation (F)	16 healthy ♂	31
R92 10 98	BIOEQUIVALENCE: Single Dose, Randomized, Two-way Crossover	3.75 mg IM, clinically tested formulation (C) 3.75 mg IM, clinically tested formulation (D)	12 healthy ♂	33
Iven's Opinion	ABSOLUTE BIOAVAILABILITY: Open, Non-randomized, Parallel	0.5 mg IV bolus, Formulation A 3.75 mg IM, q28dx4-6, Formulation C	12 ♀ endometriosis 7 ♀ uterine myoma	35
DEB-95-TRI-03	HEPATIC & RENAL INSUFFICIENCY: Open, Single Dose, Non-Randomized, Parallel	0.5 mg IV bolus, Formulation A	6 healthy ♂ 6 mod.renal imp ♂ 6 sev.renal imp. ♂ 6 hep.imp ♂	36
Millar's Opinion	COMPARATIVE PK: Single Dose, Crossover	1,5,7,10,15,20,40µg/h x 1 hour triptorelin 10,50,70,100,150,200,400 µg/h x 1 hour GnRH	7 healthy ♂	38

A. Single Dose

The pharmacokinetic (PK) parameters after IM administration of the to-be-marketed formulation of 3.75 mg Decapeptyl™ depot formulations are included in Table 5.

Table 5. Mean ±SD Pharmacokinetic Parameters after IM Administration (Tmax = median (range))

Study	Cmax (ng/ml)	Tmax (h)	AUC (ng*h/ml)
DEB-95-TRI-02	28.4 ± 7.3	1.0 [redacted]	223.15 ± 46.96
DEB-93-TRI-05*	5.87 ± 2.65	4.0 [redacted]	151.7 ± 64.5

*The blood sampling scheme in Study DEB-93-TRI-05 did not include sampling from 0-4 hours postdose. Therefore, the true Cmax, Tmax and AUC are not assessed in this study.

Reviewer Comment:
The difference in PK parameters reported in these studies are likely due to the differences in sample times.

B. Multiple Dose
The multiple dose pharmacokinetics of the clinical and proposed to-be-marketed formulations of Decapeptyl™ were not assessed.

Reviewer Comment:
1. *Due to the release profile of the to-be-marketed formulation, i.e. after an initial spike in plasma triptorelin concentrations, the concentrations are maintained at comparatively low levels over a substantial portion of the dosing interval (last 26 days), accumulation of triptorelin upon chronic dosing is probably not a significant issue.*

2. *It is the experience of the FDA with similar compounds (LHRH analogues), administered by a similar route that accumulation of LHRH analogs on multiple administration does not occur.*

C. Bioavailability
The absolute bioavailability of triptorelin was assessed in the study named, IVEN'S EXPERT OPINION. The pharmacokinetic parameters from the 0.5 mg dose administered by IV administration and the 3.75 mg depot by IM administration are included in Table 6.

Table 6.

	Cmax (ng/ml)	Tmax (h)	AUC (ng*h/ml)	t½ (h)	Cl (ml/min)	Vss (L)	% elimin. urine	F(%)
0.5 mg IV	115.8±59.0	0.03 [redacted]	81.9±32.9	5.37±2.29	110±40	32.9±16.8	20±10	
3.75 mg Depot	3.27±2.37	4 [redacted]	232.0±104.5	—	—	—	—	36.4

Reviewer Comment:
The 3.75 mg depot formulation used in "IVEN'S EXPERT OPINION" is NOT the to-be-marketed formulation.

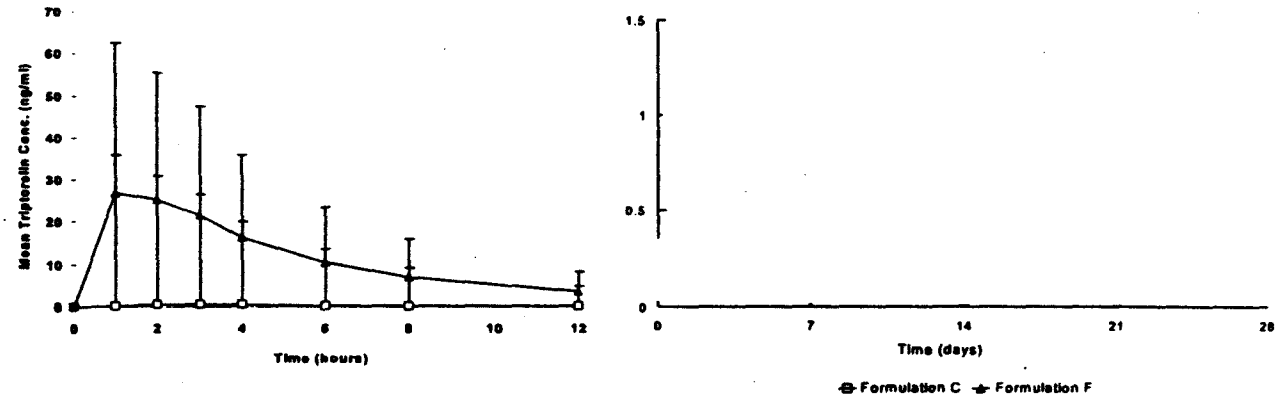
D. Bioequivalence
The bioequivalence of Decapeptyl™ formulations was determined in Studies DEB-95-TRI-02, DEB-93-TRI-05 and R92.10.98, however Study R92.10.98 does not provide relevant information and is not described. In Study DEB-95-TRI-02 the bioequivalence of the to-be-marketed formulation (Formulation F) and the formulation used predominantly in the pivotal clinical studies was determined in 24 subjects. The pharmacokinetic parameters and statistical analysis (90% confidence interval on log transformed data) from this study are included in Table 7.

Table 7.

Formulation	Cmax (ng/ml)	AUC (h*ng/ml)	Tmax (h)	Tmin (h)
Formulation C	1.03 ± 0.50	133.34 ± 45.43	4.5 [redacted]	228.0
Formulation F	28.43 ± 7.31	223.15 ± 46.96	1.0 [redacted]	96.0
90% confidence interval	**2442 - 3646**	**156 - 196**		

The plasma concentration versus time profiles are included in Figure 2.

Figure 2.



A second study (Study DEB-93-TRI-05) including 16 subjects, assessed the bioequivalence of the to-be-marketed formulation (Formulation F) and an additional formulation used in the pivotal clinical trials (Formulation D). The pharmacokinetic parameters (± SD, Tmax = median (range)) and the 90% confidence intervals on log transformed parameters are included in Table 8.

Table 8.

Formulation	C_{4h} (ng/ml)	AUC (ng*h/ml)
Formulation D	5.19 ± 2.92	190.9 ± 78.25
Formulation F	5.87 ± 2.65	151.7 ± 64.5
90% confidence interval	**93 - 152**	**68 - 94**

Reviewer Comment:

1. *The to-be-marketed formulation (Formulation F) is NOT bioequivalent to the clinically tested formulations (Formulation C and D).*

2. *The AUC and Cmax estimates from Formulation F from Studies DEB-95-TRI-02 and Study DEB-93-TRI-05 are significantly different between studies. The reason for these inter-study differences is likely to be inadequate blood sampling times from time 0-4 hours post-dose in Study DEB-93-TRI-05.*

E. Metabolism

After IV administration of triptorelin to six healthy male volunteers (Study DEB-95-TRI-03), it was determined that ≈42% of the dose was excreted in the urine unchanged. The metabolism of triptorelin is primarily by hydrolysis of the C-terminal amino acids.

The substitution of D-tryptophan at the sixth position of endogenous LHRH to form triptorelin increases resistance to cleavage by proteolytic enzymes, decreasing the metabolic clearance. The reduction in clearance between radiolabeled triptorelin and endogenous LHRH was proven in the study named, MILLAR'S EXPERT OPINION and the results of this study are included in Table 9.

Table 9.

	Endogenous LHRH	Triptorelin
t½ (min)	8.2 ± 1.2	20.0 ± 2.5
Cl (ml/min)	1538 ± 88	474 ± 32

It should be noted that the metabolite plasma concentration versus time profiles are very difficult to assess due to the nature of the molecule (decapeptide).

F. Protein Binding

The sponsor reports that endogenous LHRH and leuprolide (Lupron®) are ≈10-20% bound to plasma and that nafarelin (Synarel®) is more extensively bound to plasma (70-80%). However, *in vitro* protein binding studies using plasma from six healthy male volunteers (Study DEB-95-TRI-02) showed no binding of triptorelin to albumin. Therefore, the sponsor concluded that the triptorelin does not bind to the sera of the volunteers tested.

Reviewer Comment:

Since the sponsor only assessed the binding of triptorelin to albumin and no assessment of other potential binding in serum (serum hormone binding globulin, etc.) was made, the binding of triptorelin in plasma has not been properly assessed.

G. Special Populations

The pharmacokinetic parameters after single IV bolus administrations of 0.5 mg doses of triptorelin to six healthy male volunteers, six male patients with moderate renal insufficiency, six male patients with severe renal insufficiency and six male patients with impaired liver function are included in Table 10.

Table 10.

Study Group	Cmax (ng/ml)	Tmax (h)	AUC (h*ng/ml)	t½ (h)	Clp (ml/min)	Vss (L)	% elim. Urine	Cl renal (ml/min)	Clcreat (ml/min)
healthy	48.2±11.8	0.08	36.1±5.8	2.85±0.55	211.9±31.6	31.4±4.92	41.7±12.1	90.6±35.3	149.9±7.3
Moderate Renal Insufficiency	45.6±20.5	0.08	69.9±24.6	6.69±1.54	120.0±45.0	46.5±12.8	18.8±8.1	23.3±17.6	39.7±22.5
Severe Renal Insufficiency	46.5±14.0	0.08	88.0±18.4	7.81±1.75	88.6±19.7	47.6±8.4	4.8±3.3	4.3±2.9	8.9±6.0
Hepatic Insufficiency	54.1±5.3	0.08	131.9±18.1	7.65±1.14	57.8±8.0	35.0±5.10	62.3±4.5	35.9±5.0	89.9±15.1

Graphical representation of the serum triptorelin versus time profile in the healthy subjects and the renally impaired subjects and patients with hepatic insufficiency are included in Figures 3 and 4, respectively.

Figure 3.

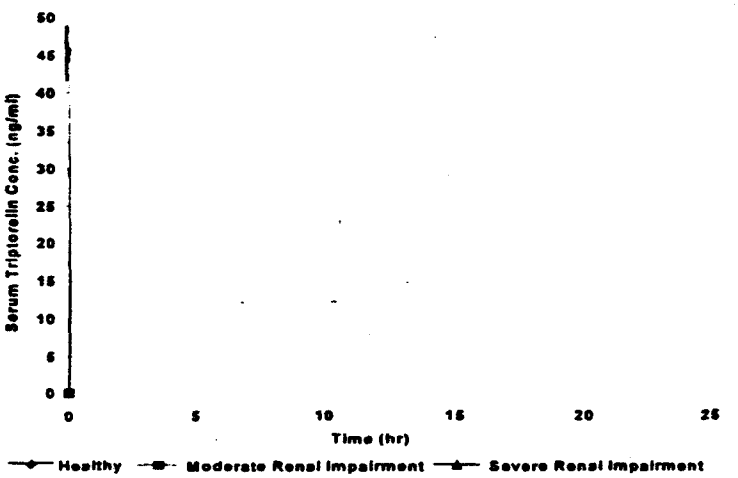
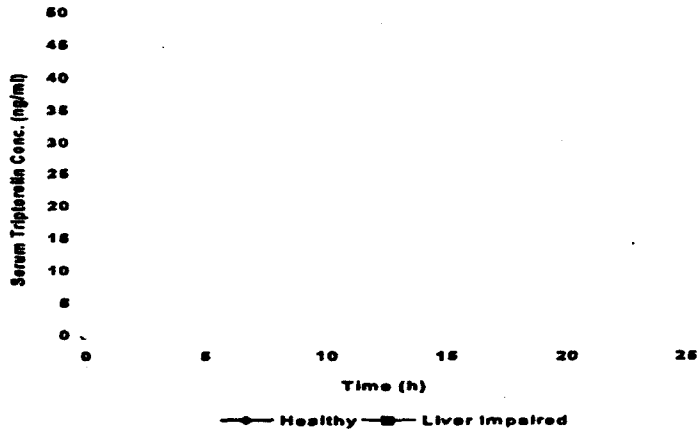


Figure 4.



Reviewer Comments:

1. *It is apparent from these data that triptorelin clearance decreases with increasing renal dysfunction and is markedly decreased in patients with liver impairment.*

2. *Only patients with liver impairment were rated as A or B on the Child's Pugh score were included in this study.*

3. *It appears from these data that the liver, rather than the kidneys, plays a more predominant role in triptorelin clearance.*

4. *The clinical significance of the changes in triptorelin pharmacokinetics in subjects with hepatic and renal function is unknown. However, due to the prolonged release and relatively low serum concentrations of triptorelin over a significant portion of the proposed dosing interval that result from administration of the depot formulations of Decapeptyl™, it the opinion of this reviewer that hepatic and renal insufficiency is of little clinical significance.*

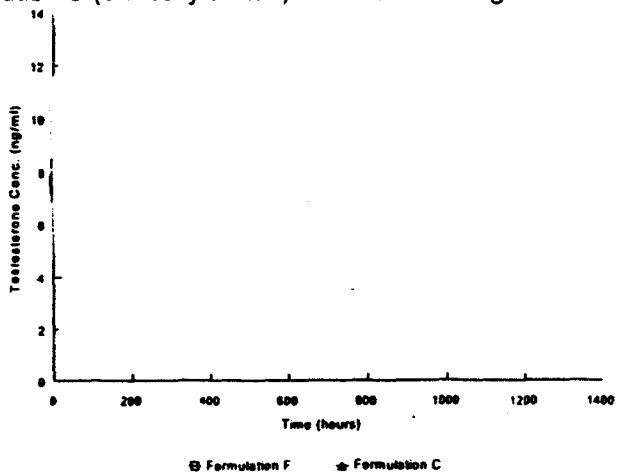
H. Drug Interactions

No drug interactions with Decapeptyl™ have been assessed. However, the sponsor indicates that hyperprolactinemic drugs should not be co-administered with Decapeptyl™ since they reduce the level of pituitary GnRH receptors.

IX. Pharmacodynamics

The clinical endpoint used to assess the efficacy of LHRH analogs in the palliative treatment of advanced prostate cancer is the suppression and maintenance of suppression of serum testosterone levels. The suppression of testosterone levels after single administrations of the to-be-marketed formulation and the formulations used in the pivotal clinical trials were compared in Studies DEB-95-TRI-02 and DEB-93-TRI-05. The serum testosterone concentration versus time profile after administration of Formulation F (to-be-marketed) and Formulation C (clinically tested) is included in Figure 5.

Figure 5



Statistical analysis by classical 90% confidence interval (ANOVA) indicated that the maximum testosterone concentration and area under the serum testosterone concentration versus time curve after single administrations of the formulations used in Study DEB-95-TRI-02 (Formulations F and C) and in Study DEB-93-TRI-05 (Formulations F and D) were equivalent.

The lone multiple dose study (two administrations of Decapeptyl™) in advanced prostate cancer patients submitted to the OCPB/DPEII for review was Study 914CL27R (review of this study is in Attachment 3, page 40). This study attempted to assess a dose-response relationship for Decapeptyl™ and testosterone suppression. The serum testosterone concentration versus time profiles of 1.9, 3.75 and 7.5 mg doses of triptorelin (NOT the to-be-marketed) are included in Figure 6. The number of patients in which testosterone levels were not maintained below 1.75 nmol/L (previously determined castrate range) after 31 days post-dose are included in Table 11. It should be noted that the serum triptorelin concentrations were not submitted.

Figure 6.

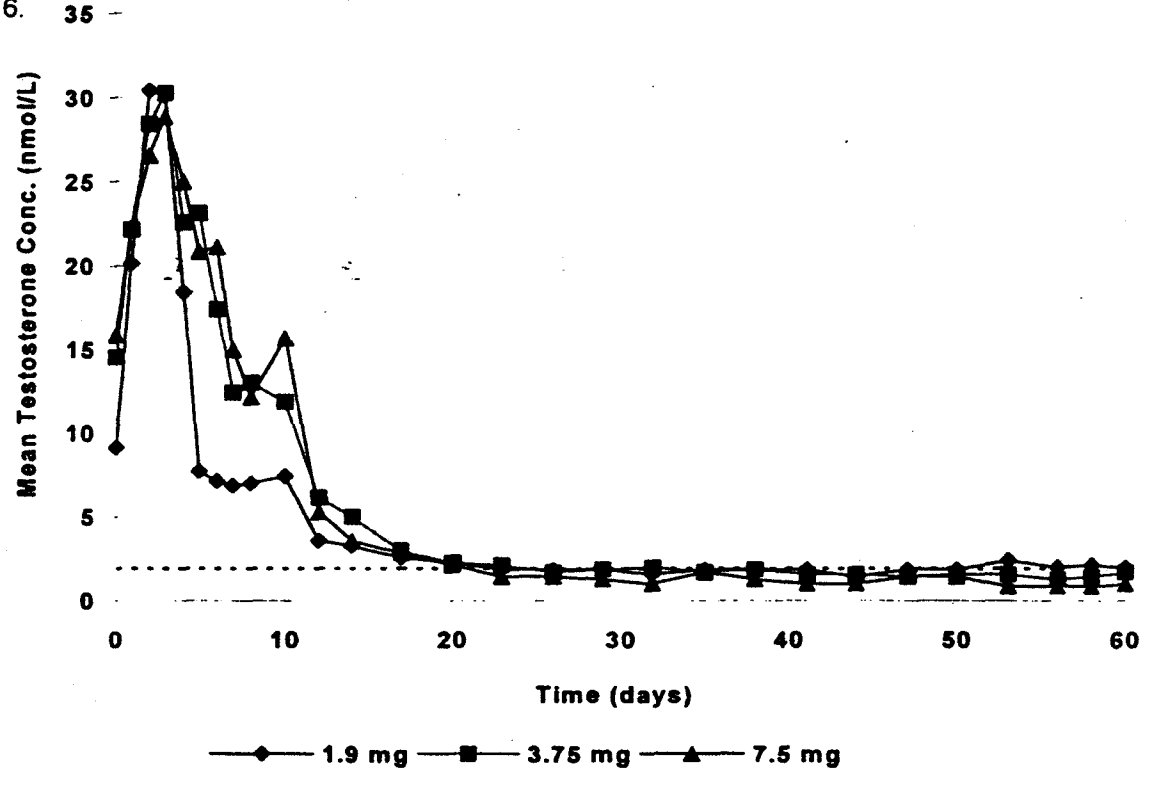


Table 11. Escape from Castrate Levels

Dose	n	# patients escaped above 1.75 nmol/L
1.9 mg	5	3
3.75 mg	5	5
7.5 mg	4	1

A record of escapes from castrate range (<1.735 nmol/L) of testosterone concentrations from long term clinical trials (intent-to-treat population of Studies 914CL14P, 914CL7P and 914CL17E) are included in Table 12. It should be noted that these studies were not submitted to OCPB/DPEII for review.

Table 12.

	Decapeptyl™		Orchiectomy		P-value
	N/total	%	N/total	%	
Baseline	138/145	95.2	91/96	94.8	1.000
Month 1	34/128	26.6	22/85	25.9	0.912
Month 2	24/127	18.9	15/66	22.7	0.530
Month 3	19/120	15.8	18/76	23.7	0.171
Month 6	19/105	18.1	10/67	14.9	0.588
Month 9	14/94	14.9	16/65	24.6	0.123
Month 12	12/75	16.0	10/49	20.4	0.530
Month 15	15/62	24.2	8/27	29.6	0.590
Month 18	14/49	28.6	8/22	36.4	0.511
Month 21	10/38	26.3	3/19	15.8	0.510
Month 24	8/32	25.0	3/15	20.0	1.000

Reviewer Comments:

1. *Secondary flare of testosterone levels upon chronic administration of Decapeptyl™ has not been assessed. Additionally, the pharmacokinetic profile of Formulation F is probably more conducive to a secondary flare due to the spike triptorelin levels that do not occur after administration of Formulations C and D (see Figure 2, **Pharmacokinetic** section, above). Therefore, the sponsor's use of pharmacodynamic equivalence in the linkage between the to-be-marketed formulation (F) and the clinically tested formulations (C and D) after single doses is problematic.*

2. *The castrate range (<1.75 nmol/L) has been constructed by the measurement of testosterone levels is orchiectomized patients. Therefore, the observation made in the clinical studies, that up to 36% of the orchiectomized patients escaped is perplexing. It was stated by Dr. Dan Shames, Medical Officer, Division of Reproductive and Urologic Drug Products that although patients are listed as orchiectomized, it is possible that some of the patients were only partially orchiectomized. This would account for the apparent escapes from castrate range in these patients.*

3. *Additionally, the testosterone assay validation from the clinical studies listed above are not presented. Therefore, the confidence one can have in these data is limited and could also be the reason for the relatively high testosterone levels after orchiectomy (apparent escapes from castrate levels).*

4. *Although the proposed to-be-marketed formulation of Decapeptyl™ was not used, the pharmacodynamic study assessing the testosterone suppression after administration of 1.9, 3.75 (proposed dose) and 7.5 mg doses of triptorelin indicates that no dose response (PK/PD) assessment can be made at these doses.*

X. Labeling

Attachment 1 includes the sponsor's proposed labeling.

Labeling Comments:

1. The ***Absorption*** subsection of the **Pharmacokinetic** section of the labeling appropriately uses the pharmacokinetic parameters from the to-be-marketed formulation from Study DEB-95-TRI-02. However this study is a bioequivalence study between the clinically tested triptorelin acetate depot formulation and the to-be-marketed triptorelin pamoate formulation and does not include an IV bolus dose of triptorelin. Therefore, it is unclear how the absolute bioavailability (■%) has been assessed from these data and this information should be deleted.

2. Since the pharmacokinetic parameters are included in Table 1 in the ***Absorption*** subsection of the **Pharmacokinetics** section of the labeling, the sponsor should remove these parameters from the first paragraph in the same subsection.

3. Since the plasma binding of triptorelin has not been adequately assessed, the ***Distribution*** subsection of the **Pharmacokinetics** section of the labeling should be changed to the following;

Draft

APPEARS THIS WAY
ON ORIGINAL

7 pages redacted from this section of the approval package consisted of draft labeling

XII. Attachment 2: Individual Pharmacokinetic Study Reviews

Study Number: DEB-95-TRI-02

Title: Pharmacodynamic equivalence study of two triptorelin sustained released formulations: pamoate lyophilized vs. Acetate non lyophilized after intramuscular administration in healthy volunteers.

Objectives: The primary objective was to evaluate the equivalence of the pharmacokinetics and pharmacodynamics of two triptorelin sustained-release formulations after intramuscular administration in healthy volunteers by measuring serum testosterone levels.

Design: The study was a single dose, open, randomised, balanced, crossover design.

Investigators and Location:

Subjects: Twenty four healthy male volunteers aged 19-54 years participated in the study. Twenty subjects completed the study as per the randomisation code.

Formulations: Two sustained-release formulations (acetate microsphere non-lyophilized and pamoate microgranule lyophilized) of triptorelin were administered. It should be noted that Formulation F is the to-be-marketed formulation and Formulation C is the predominantly used formulation in the pivotal clinical trials.

Table 1.

	Formulation C: Triptorelin acetate microspheres	Formulation F: Lyophilized triptorelin pamoate microgranules
Triptorelin (mg)	3.75	3.75
50:50 (d,l-lactide-co-glycolide) (mg)	185	170
mannitol (mg)	—	85
Carboxymethylcellulose Na (mg)	40	30
Polysorbate 80 (mg)	20	2

Dosages and Administration: A single intramuscular injection of each formulation was given at intervals of at least 12 weeks.

Sample Collection: Blood samples were collected at times 0, 1, 2, 3, 4, 6, 8 and 12 hours post dose and Days 2, 3, 4, 5, 6, 7, 8, 15, 22, 29, 36, 43 and 57 for each session.

Assay: Triptorelin levels were determined by a radioimmunoassay using [redacted] human serum samples and the validation is presented in Table 2, below.

Table 2. Triptorelin Assay Validation

Sensitivity	[redacted] ng/ml	
Intra-assay CV	[redacted] %	
Inter-assay CV	[redacted] %	
Cross-reactivity	D-trp^6-desGly^{10}Pro^{9}EA-GnRH	[redacted] %
	"all other similar peptides"	[redacted] %

Serum Testosterone levels were determined be a radioimmunoassay and the validation is presented in Table 3, below.

Table 3. Testosterone Assay Validation

Sensitivity	[redacted] nmol/L	
Intra-assay CV	[redacted] %	
Inter-assay CV	[redacted] %	
Cross-reactivity	dihydrotestosterone 5α-androstane-3,17β-diol other steroids	[redacted] % % %

Results:

Pharmacokinetics

Mean (+ SD) triptorelin concentrations are depicted in Figure 1 and the mean (± SD) pharmacokinetic parameters are included in Table 4.

Figure 1

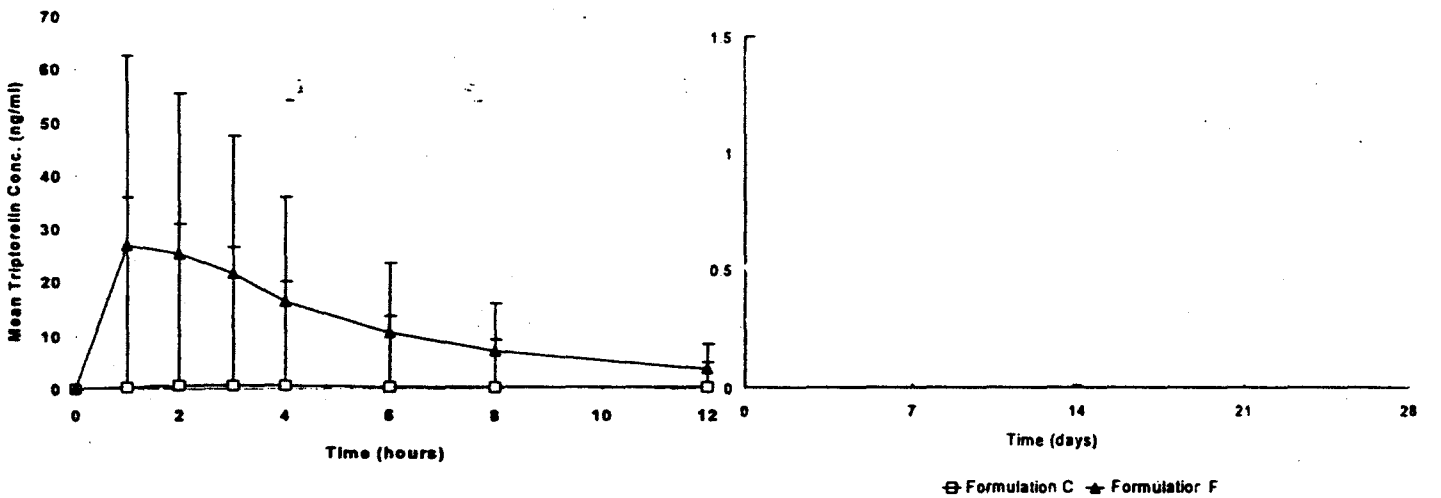


Table 4.

Formulation	Cmax (ng/ml)	Tmax (h)	AUC (h*ng/ml)	Tmin (h)
Formulation C	1.03 ± 0.50	4.5 [redacted]	133.34 ± 45.43	228.0
Formulation F	28.43 ± 7.31	1.0 [redacted]	223.15 ± 46.96	96.0

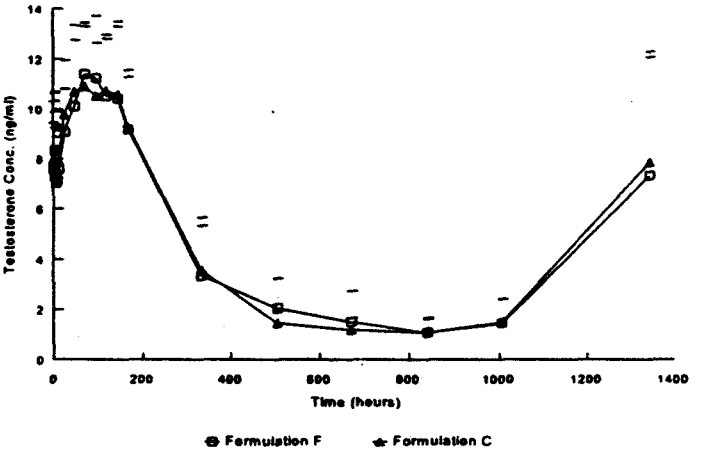
Pharmacodynamics

The mean (+ SD) pharmacodynamic parameters (testosterone pharmacokinetics) of Decapeptyl™ are included in Table 5 and the mean plasma testosterone concentrations resulting from each formulation are included in Figure 2.

Table 5.

Formulation	Cmax (nmol/L)	Tmax (h)	AUC (h*nmol/l)	Cmin (nmol/l)	Tcast (h)
Formulation C	42.29 ± 8.70	96.0 [redacted]	12011.9 ± 2908.4	3.33 ± 1.28	588.0
Formulation F	44.52 ± 10.68	96.0 [redacted]	12504.6 ± 2661.1	3.12 ± 0.90	672.0

Figure 2.



Statistics
Based on Log-transformed data the 90% confidence interval for the AUC and Cmax for both triptorelin and testosterone are included in Table 6.

Table 6.

	Triptorelin 90% CI	Testosterone 90% CI
AUC	1.56 - 1.96	0.98 - 1.12
Cmax	24.42 - 36.46	0.98 - 1.12

Other Assessments
There was no clinically significant difference in the adverse event profile between the 2 formulations except in the incidence of decreased libido which was almost double after triptorelin acetate when compared to triptorelin pamoate.

Reviewer Comments:

1. Formulation "C", identified as the predominant formulation used in the pivotal clinical studies (#914CL14P, #914CL17E and #914CL7P) used in Study DEB-95-TRI-02, was not manufactured by the same manufacturer as the batches used in the clinical studies. Additionally, only 2 of 24 batches used in the pivotal clinical trials were manufactured with the same process as that used to manufacture the formulation "C" used in Study DEB-95-TRI-02.

2. Formulation C, used in the pivotal clinical trial is NOT bioequivalent with the to-be-marketed formulation Formulation F.

3. Although the testosterone AUC and Cmax values for the to-be-marketed formulation (F) and the clinically tested formulation (C) are statistically equal after single administrations, the statistical rigor of this comparison is questionable. Additionally, the rate of escapes of testosterone levels out of "castrate" range upon chronic dosing of the formulations tested herein is unknown. Therefore, the therapeutic equivalence can not be established with these data.

4. Plasma triptorelin levels from both formulations returned to zero in all subjects prior to Day 28 post-dose. Since the proposed dosing interval of Decapeptyl™ is 28 days, no accumulation of triptorelin is expected upon chronic dosing.

Study Number: 017-001

Study Title: A Bioequivalency Study of Two Sustained-Release Formulations of Decapeptyl™ in Patients With Advanced Prostatic Carcinoma

Investigator:

Objectives: The objective of the study was to determine the bioequivalence of two formulations of Decapeptyl™: a microgranule formulation of the acetate salt and a microsphere formulation of a pamoate salt.

Study Design: This was a two-way, randomized, double-blind, comparative investigation of two formulations in three treatment cycles with a formulation crossover after two cycles were completed.

Blood Sampling: Samples for triptorelin and testosterone determination were taken during house calls on days 2, 4, 7, 14, 21, and 28.

Subjects: Thirty (30) patients with advanced prostatic cancer were enrolled and randomly assigned to one of two treatment groups. A total of 29 patients completed the study (Patient #2 died of non-drug related gastrointestinal perforation on Day 42, Cycle 2) and 28 were included in the bioequivalence analysis (Patient #6 was excluded because the study medication was improperly administered in Cycle 1).

Formulations:
The formulations used in this study are included in Table 7. It should be noted that Formulation C is the formulation used in pivotal clinical trials 914CL14P, 914CL17E, 914CL7P.

Table 7.

	Formulation C: Triptorelin acetate microspheres	Formulation E: Triptorelin pamoate microgranules
Triptorelin (mg)	3.75	3.75
50:50 (d,l-lactide-co-glycolide) (mg)	185	170
Carboxymethylcellulose Na (mg)	40	40
Polysorbate 80 (mg)	20	20

Duration of Treatment: The following formulation dosing regimens were used and the total study time was 84 days:

Formulation C; Formulation C; Formulation E (CCE) - an injection of Formulation C was given once every 28-days for two cycles, then the subjects were crossed over to receive an injection Formulation E.

Formulation E; Formulation E; Formulation C (EEC) - an injection of Formulation E was given once every 28-days for two cycles, then the subjects were crossed over to receive an injection Formulation C.

Analytical Methodology:
Serum testosterone levels were determined by a direct radioimmunoassay with rabbit polyclonal antiserum raised against testosterone-3-CMO-BSA. However, validation of the testosterone assay used herein was not submitted.

Plasma Decapeptyl™ levels were determined by a radioimmunoassay (RIA). The validation of the assay is included in Table 8.

Table 8.

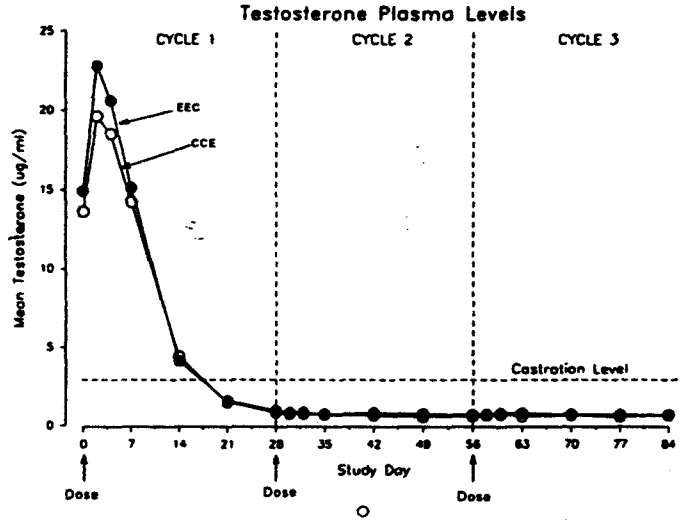
Sensitivity	— pg/ml		
Target values	375 pg/ml	750 pg/ml	1500 pg/ml
Accuracy (recovery)	—	—	—
Intraassay Precision (% CV)	—	—	—
Interassay Precision (% CV)	—	—	—

Results:

Pharmacodynamics

The mean plasma testosterone levels are illustrated in Figure 3.

Figure 3. Plasma Testosterone Concentration versus Time Curves



The mean (± SD) pharmacokinetic (pharmacodynamic) parameters of testosterone are included in Table 9.

Table 9. Testosterone Bioequivalence Crossover Cycle 2 and Cycle 3

	t_{cast} (hr)	AUC_{0-t} (nmol/L•day)	AUC_{0-com} (nmol/L•day)	C_{max} (nmol/L)	t_{max} (day)
	Cycle 1 (n=14)	Cycles 2 and 3 (n=28)			
Formulation C (mean ± SD)	486 ± 97.3	2.7 ± 0.7	2.2 ± 0.8	-0.2± 0.5	4.9 ± 5.4
Formulation E (mean ± SD)	456 ± 102.7	2.7 ± 0.5	2.2 ± 0.6	-0.2 ± 0.6	5.3 ± 5.5
Two One-Sided C.I.	–	0.89-1.19	0.85-1.19	0.84-1.13	0.66 - 1.83
Westlake's C.I.	–	1.35	2.40	21.16	6.2
ANOVA p value power	–	0.7081 0.96	0.9897 0.93	0.7743 0.50	0.8072 0.99

**AUC_{0-t}, AUC_{0-com} (AUC over a common time interval for Cycles 2 and 3) and Cmax based on log transformed data

Additional pharmacodynamic information is included in Tables 10 and 11, below.

Table 10. Summary of FSH, LH and PAP Levels (mean ± SE)

Parameter		Mean Levels			
Sequence Group	N	Baseline	Cycle 1*	Cycle 2*	Cycle 3*
FSH (U/L)					
CCE	14	7.6 ± 1.0	2.9 ± 0.4	4.3 ± 0.5	4.6 ± 0.5
EEC	14	11.0 ± 2.2	3.0 ± 0.4	4.2 ± 0.5	4.9 ± 0.5
LH (U/L)					
CCE	14	2.6 ± 0.4	0.2 ± 0.02	0.1 ± 0.0	0.1 ± 0.0
EEC	14	4.4 ± 0.9	0.7 ± 0.4	0.1 ± 0.0	0.1 ± 0.0
Acid Phosphatase (U/L)					
CCE	28	41.8 ± 13.4	19.3 ± 9.1	14.2 ± 8.0	10.1 ± 4.5
EEC	28	34.8 ± 17.3	9.2 ± 2.7	5.8 ± 1.3	5.3 ± 1.2

*No statistically significant differences between the two sequence groups for each of the three parameters ($p > 0.05$).

Table 11. Performance Scale Results

Formulation Dosing Sequence	Scale	Day 0		Day 28		Day 56		Day 84	
		n	%	n	%	n	%	n	%
CCE	0	6/15	(40)	6/15	(40)	7/15	(47)	7/15	(47)
	1	5/15	(33)	6/15	(40)	5/15	(33)	4/15	(27)
	2	1/15	(7)	0/15	(0)	0/15	(0)	1/15	(7)
	3	3/15	(20)	2/15	(13)	2/15	(13)	3/15	(20)
	4	0/15	(0)	1/15	(7)	1/15	(7)	0/15	(0)
EEC	0	9/15	(60)	8/15	(53)	8/14	(57)	8/14	(57)
	1	3/15	(20)	4/15	(27)	5/14	(36)	5/14	(36)
	2	2/15	(13)	1/15	(7)	0/14	(0)	0/14	(0)
	3	1/15	(7)	1/15	(7)	1/14	(7)	1/14	(7)
	4	0/15	(0)	1/15	(7)	0/14	(0)	0/14	(0)

Pharmacokinetics:
The mean (±SD) pharmacokinetic parameters (triptorelin) from this study are included in Table 12. The 90% CI was calculated with natural log (ln) transformed AUC and Cmax.

Table 12.

	AUC0-com (h*ng/ml)	Cmax (ng/ml)	Tmax (h)
Formulation C	12919.6 ± 8217.5	1545.1 ± 1137.7	168
Formulation E	8534.3 ± 5010.6	1358.9 ± 1015.8	48
90% CI	64 - 74	77 - 96	

Sponsor's Conclusions:

1. Immediately after the first dose of Decapeptyl™, plasma testosterone levels increased and then decreased rapidly over 21 days. Plasma testosterone levels remained suppressed and comparable between the two formulations during Cycles 2 and 3.

2. The two Decapeptyl™ formulations tested herein were comparable with respect to the effect on testosterone AUC_{0-t}, AUC_{0-com}, t_{max} and C_{max} as shown by the Shuirmann Two One-Sided t-Test C.I.s. However, since the statistical power to assess a difference in testosterone Cmax was low (50%), ANOVA could not be used.

Reviewer Comments:

1. Neither of the formulations used in this study (Formulation C or E) is the to-be-marketed formulation.

2. The formulations used in this study (Study 017/001), Formulations C (primary formulation used in the pivotal clinical trials) and Formulation E are not bioequivalent.

3. Formulation E, tested herein, was not used in any of the pivotal clinical trials.

4. The validation of the RIA used herein to estimate serum testosterone levels was not submitted. Therefore, the confidence one can have in the testosterone data presented herein is limited.

Study Number: DEB-93-TRI-05

Title: Study of comparative bioavailability and pharmacodynamics of two triptorelin sustained release formulations after IM administration in healthy subjects

Objectives: To evaluate the bioavailability and the pharmacological effects of two triptorelin formulations.

Design: The study was a single dose, open, randomised, balanced, crossover design.

Investigators and Location: [redacted]

Subjects: Sixteen healthy male volunteers aged 25-45 years participated in the study.

Formulations: Two sustained-release formulations (acetate microsphere lyophilized and pamoate microgranule lyophilized) of triptorelin were administered. It should be noted that the lyophilized triptorelin pamoate formulation (Formulation F) is the to-be-marketed formulation.

Table 13.

	Formulation D: Lyophilized Triptorelin acetate microspheres	**Formulation F: Lyophilized triptorelin pamoate microgranules**
Triptorelin (mg)	3.75	**3.75**
50:50 (d,l-lactide-co-glycolide) (mg)	185	**170**
mannitol (mg)	85	**85**
Carboxymethylcellulose Na (mg)	30	**30**
Polysorbate 80 (mg)	20	**2**

Dosages and Administration: A single intramuscular injection of each formulation was given at intervals of at least 12 weeks.

Sample Collection: Plasma samples for triptorelin and testosterone determinations were collected at times 0, 4, 8 and 12 hours on Day 1 and the mornings of Days 2, 3, 8, 15, 22, 29, 36, and 43 after dosing.

Assay: Triptorelin levels were determined by a radioimmunoassay using [redacted] human serum samples and the validation is presented in Table 14, below.

Table 14. Triptorelin Assay Validation

Sensitivity	[redacted] ng/ml
Intra-assay CV	[redacted] %
Inter-assay CV	[redacted] %
Cross-reactivity	No data available

Serum Testosterone levels were determined be a radioimmunoassay and the validation is presented in Table 15, below.

Table 15. Testosterone Assay Validation

Sensitivity	[redacted] nmol/L
Intra-assay CV	[redacted] %
Inter-assay CV	[redacted] %
Cross-reactivity	No data available

Results:

Pharmacokinetics

The triptorelin pharmacokinetic parameters are included in Table 16.

Table 16.

Formulation	Cmax (ng/ml)	Tmax (h)	AUC (h*ng/ml)
Formulation D	5.19 ± 2.92	4 [redacted]	190.9 ± 78.25
Formulation F	5.87 ± 2.65	4 [redacted]	151.7 ± 64.5

Pharmacodynamics

Testosterone parameters after triptorelin administration are included in Table 17.

Table 17.

Formulation	Cmax (nmol/L)	Tmax (h)	AUC (h*nmol/l)	Cmin (nmol/l)	Tcast (h)
Formulation D	43.29 ± 8.75	48 [redacted]	12981 ± 2952	1.23 ± 0.39	791 [redacted]
Formulation F	45.66 ± 9.20	48 [redacted]	13450 ± 2939	1.39 ± 0.37	822 [redacted]

Statistics

Based on Log-transformed data the 90% confidence interval for the AUC and Cmax for both triptorelin and testosterone are included in Table 18.

Table 18.

	Triptorelin 90% CI	Testosterone 90% CI
AUC	68 - 94	95 - 113
Cmax	93 - 152	97 - 115

Reviewer Comments:

1. Formulation D, used in one of the pivotal clinical trials (#52014 ST 8040, [redacted] is **NOT** bioequivalent with the to-be-marketed formulation, Formulation F.

Study Number: R92.10.98

Title: Study of comparative bioavailability, pharmacological effects and tolerance of two triptorelin sustained release formulations: A new thermostable lyophilized formulation versus the reference formulation, after single intramuscular administration in twelve normal healthy volunteers

Objectives: The objective of the study was to evaluate the bioequivalence, by measuring plasma levels of triptorelin and serum levels of testosterone as a measure of the pharmacological response of two Triptorelin sustained release formulations after single intramuscular administration in twelve male healthy volunteers.

Study Design: This was a single dose, open, two way, randomized study

Formulations:
Formulation C: Triptorelin acetate microspheres syringes (Decapeptyl™ 3.75 S.R.) dosed at 3.75 mg per syringe (quantity of triptorelin injected 3 mg)

Formulation D: Triptorelin thermostable lyophilized acetate microspheres vials dosed at 4.20 mg per vial (quantity of triptorelin injected 3 mg)

Analytical methods
Triptorelin plasma levels were determined by RIA. The analytical determinations were performed by [redacted]

The testosterone was evaluated using a RIA method by [redacted]

Statistical analysis
The values of parameters AUC and Cmax, were compared after the logarithmic transformation of the data. The following analysis were carried out:

ANOVA, confidence intervals of 90%
Two-one side t-test, (80-125)

The values of tmax and Tlag were evaluated by means of a non-parametric (3) analysis using the tmax and Tlag differences,90%confidence intervals.

Results:
Pharmacokinetics
The pharmacokinetic parameters and statistical analysis from plasma triptorelin levels from Formulations C and D are included in Table 19.

Table 19.

Formulation	Cmax (ng/ml)	Tmax (h)	AUC (ng*h/ml)
Formulation C	5.79 ± 2.22	2 [redacted]	289 ± 78
Formulation D	8.96 ± 2.26	1 [redacted]	285 ± 60
90 %CI	129 - 208		89.0 - 113

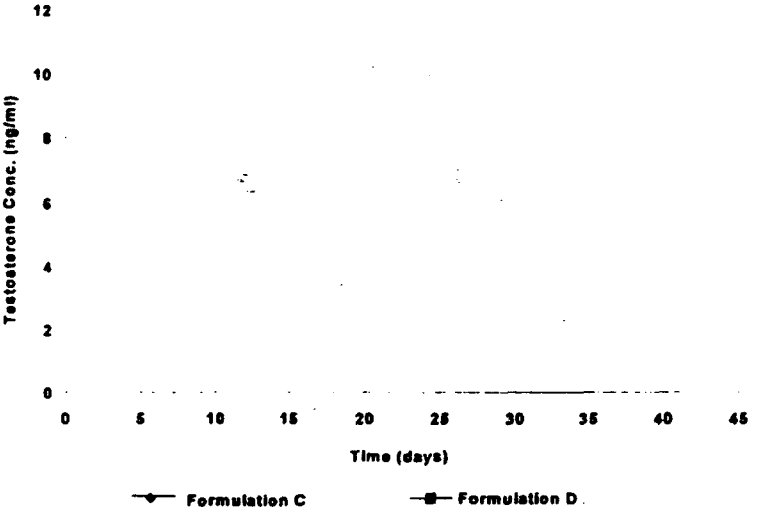
Pharmacodynamics

The primary pharmacodynamic endpoint for LHRH analogs is the suppression and maintenance of suppression of serum testosterone levels. The measurement of initial flare of serum testosterone (Cmax) and the time to reach castrate levels of testosterone (tcast) are included in Table 20. Additionally, the serum testosterone concentration versus time profiles after administration of Formulation N and L are included in Figure 4.

Table 20.

Formulation	Cmax (nmol/L)	Tcast (h)
Formulation C	38.3 ± 12.1	440
Formulation D	39.6 ± 16.9	426
90 %CI	91 - 111	94 - 119

Figure 4.



Conclusions:

1. The extent of absorption of triptorelin from both formulations is bioequivalent.

2. The comparison of Cmax and Tmax values of triptorelin can not allow us to conclude bioequivalence in relation with the absorption rate. The Cmax after the administration of the lyophilized form was higher than the Cmax obtained after the reference formulation.

3. No differences have been observed when the testosterone Cmax levels (as a measure of the flare-up effect) and the time required to achieve castration level were compared between formulations. This fact allows us to conclude that the differences observed in the absorption rate of triptorelin have not modified the flare-up effect and the time required to achieve the therapeutic response of the formulations studied.

Reviewer Comments:

1. Formulations C and D were the formulations used in the pivotal clinical trials, but neither formulation is the to-be-marketed formulation.

2. Formulations C and D are not bioequivalent.

"Iven's Expert Opinion"
This study was conducted by a gynecologist (Dr. H. Iven, Clinic for Gynecology and Obstetrics, Medical University of Lubeck, Lubeck, Germany) that, reportedly has extensive experience with triptorelin depot formulation.

Study Title: Pharmacokinetics of triptorelin following IV bolus injection and on the bioavailability from Decapeptyl™ depot in patients [redacted]

Objectives: To assess the bioavailability of Decapeptyl™ depot (3.75 mg) with an IV bolus injection (0.5 mg).

Study Design: This was an open, non-randomized.

Blood Sampling: Blood samples were collected for triptorelin concentrations at 2, 5, 10, 20, 30, 45, 60, 75 and 90 mins and 2, 2.5, 3, 3.5, 4, 6, 8, 10, 14 and 24 hrs after IV administration and 5, 15 and 30 mins and 1, 2, 3, 4, 6, 8 and 24 hrs and 3, 6, 9, 13, 16, 20, 23 and 27 days after the IM (depot) administration.

Subjects: 12 patients with [redacted] and 7 patients with [redacted] were enrolled in this study.

Formulations: The ingredients in the depot formulation used herein are not submitted. However, it is stated that the formulation is triptorelin acetate microspheres (3.75 mg) manufactured by Ferring. The formulation used in this study is NOT the to-be-marketed formulation.

Analytical Methodology:
Plasma Decapeptyl™ levels were determined by a [redacted] radioimmunoassay (RIA) with extraction. The validation of the assay is included in Table 21.

Table 21.

Standard Dilution	9.7 - 2500 pg/ml								
Target values (pg/ml)	9.7	19.0	39.0	78.0	156.0	312.0	625.0	1250.0	2500.0
Accuracy (% inaccuracy)	[redacted]								
Interassay Precision (% CV)	[redacted]								

Results:
The mean (±SD) pharmacokinetic parameters (triptorelin) from this study are included in Table 22.

Table 22.

	Cmax (ng/ml)	Tmax (h)	AUC (ng*h/ml)	t½ (h)	Cl (ml/min)	Vss (L)	% elimin. urine
0.5 mg IV	115.8±59.0	0.03 [redacted]	81.9±32.9	5.37±2.29	110±40	32.9±16.8	20±10
3.75 mg Depot	3.27±2.37	4 [redacted]	232.0±104.5	---	---	---	---

Sponsor's Conclusions:
1. The pharmacokinetics of triptorelin after IV bolus can be described by a 3-compartment model with a terminal t½ of ≈5 hours and a total clearance of 100 ml/min.

2. The bioavailability of triptorelin after IM administration of Decapeptyl™ is 36.4% compared to IV administration.

Reviewer Comments:
1. The formulation used herein is NOT the to-be-marketed formulation.

2. I concur with the sponsors conclusions.

Study Number: DEB-95-TRI-03

Title: Pharmacokinetic assessment of triptorelin after single intravenous bolus administration in healthy male volunteers and male patients with renal or liver insufficiency.

Objectives: To assess the effect of renal or hepatic insufficiency on the pharmacokinetics of triptorelin.

Design: Open, single-dose, non-randomized in 4 parallel groups.

Subjects:
Group I: 6 healthy male volunteers (creatinine clearance > 100 ml/min)
Group II: 6 male patients with moderate renal insufficiency (creatinine clearance of 20 to 60 ml/min)
Group III: 6 male patients with severe renal insufficiency (creatinine clearance of <20 ml/min)
Group IV: 6 male patients with impaired liver function (Child A or B) and with normal renal function (creatinine clearance >80 ml/min)

Formulation: The formulation of triptorelin used in this study was a solution for injection and is NOT the to-be-marketed formulation.

Dosages and Administration: A single IV bolus injection of 0.5 mg triptorelin acetate was administered.

Sample Collection: Blood samples for determination of triptorelin concentrations were collected at 0 (pre-dose), 0.08, 0.16, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose.

Assay: Serum triptorelin levels were determined by RIA without extraction at [redacted]

Results:
Pharmacokinetics
The triptorelin pharmacokinetic parameters are included in Table 23 and the statistical information is included in Table 24. The serum triptorelin versus time profiles in patients with various stages of renal impairment are included in Figure 5.

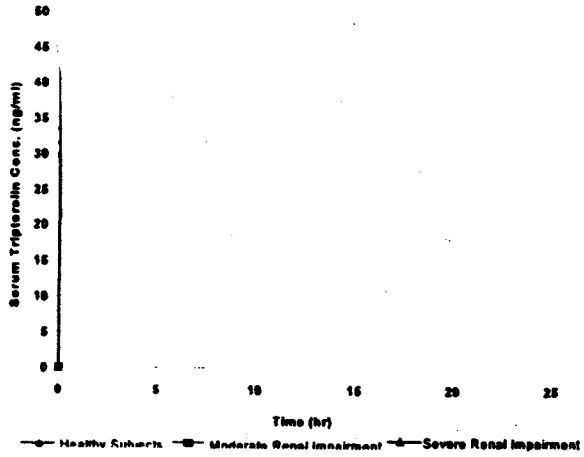
Table 23.

Study Group	Cmax (ng/ml)	Tmax (h)	AUC (h*ng/ml)	MRT (h)	t½ (h)	Clp (ml/min)	Vss (L)	% elim. Urine	Cl renal (ml/min)	Clcreat (ml/min)
Grp I	48.2±11.8	0.08	36.1±5.8	2.51±0.47	2.85±0.55	211.9±31.6	31.4±4.92	41.7±12.1	90.6±35.3	149.9±7.3
Grp II	45.6±20.5	0.08	69.9±24.6	6.65±1.20	6.69±1.54	120.0±45.0	46.5±12.8	18.8±8.1	23.3±17.6	39.7±22.5
Grp III	46.5±14.0	0.08	88.0±18.4	9.12±1.38	7.81±1.75	88.6±19.7	47.6±8.4	4.8±3.3	4.3±2.9	8.9±6.0
Grp IV	54.1±5.3	0.08	131.9±18.1	10.18±1.49	7.65±1.14	57.8±8.0	35.0±5.10	62.3±4.5	35.9±5.0	89.9±15.1

Table 24. Statistical Analysis (90% CI) for the Triptorelin Log Transformed Pharmacokinetic Parameters

	Group II/Group I	Group III/Group II	Group IV/Group I
Cmax (ng/ml)	60 - 132	72 - 157	92 - 146
AUC (ng*h/ml)	137 - 227	97 - 161	283 - 381
t½ (hr)	189 - 289	94 - 144	226 - 323

Figure 5. Serum Triptorelin Levels in Patients with Various Stages of Renal Insufficiency



Reviewer Comments:

1. A significant decrease in triptorelin clearance (increase in t½) was observed with various stages of renal insufficiency.

2. A significant decrease in triptorelin clearance (increase in t½) was observed in subjects with hepatic insufficiency.

3. It appears from these data that the liver, rather than the kidneys, plays a more predominant role in triptorelin clearance.

4. The clinical significance of the changes in triptorelin pharmacokinetics in subjects with hepatic and renal function is unknown. However, due to the prolonged release and relatively low serum concentrations of triptorelin over a significant portion of the proposed dosing interval that result from administration of the depot formulations of Decapeptyl™, it the opinion of this reviewer that hepatic and renal insufficiency is of little clinical significance.

5. The assay used to assess serum triptorelin concentrations herein, [redacted]. Therefore, the levels of triptorelin reported herein may not correlate with those from other studies where [redacted] was employed.

APPEARS THIS WAY
ON ORIGINAL

"Millar's Expert Opinion"

This "study" appears to be a manuscript prepared by Dr. R.P Millar, Medical Research Council Regulatory Peptides Research Unit, Department of Chemical Pathology, University of Cape Town Medical School and Groote Schuur Hospital, Observatory 7925, South Africa.

Title: Comparative Metabolic Clearance and Gonadotropin Releasing Activity of GnRH and D-Trp6 GnRH

Objectives: To compare the clearance of endogenous GnRH and triptorelin in healthy men.

Blood Sampling: Blood samples were collected -15, 0, 15, 30, 45, 50, 55, 60, 62, 64, 66, 68, 70, 72, 75, 78, 80, 85, 90, 105 and 120 minutes post-dose.

Subjects: 7 healthy male volunteers (aged 22-27 years) were included in this study.

Formulations: The formulation used was not included.

Analytical Methodology: Plasma Decapeptyl™ levels were determined by a radioimmunoassay (RIA) The validation of the assay is included in Table 25.

Table 25.

Sensitivity	1.3 ± 0.4 pg/tube		
Interassay Precision (%-CV)	3 (n=16)		
Cross reactivity	Antiserum 69	Antiserum 744	Antiserum 1076
D-Trp6 GnRH	100	100	<0.01
GnRH	<0.0005	100	100
D-Trp6 Pro9N-EA GnRH	120		
D-Leu6 GnRH	0.0083	54	<0.01
D-Leu6 Pro9N-EA GnRH	0.0020		<0.01
Lys8 GnRH	<0.0005	1.2	82
Pro9N-EA GnRH	<0.0005	<0.01	52
(1-2) GnRH	<0.0005		<0.01
(1-6) GnRH	<0.0005	<0.01	<0.01
(1-7) GnRH		<0.01	
(1-9) GnRH		<0.01	
(2-10) GnRH	<0.0005	100	27
(3-10) GnRH	<0.0005	100	18
(6-10) GnRH	<0.0005	37	<0.01
(7-10) GnRH	<0.0005	32	<0.01
Somastatin	<0.0005	<0.01	<0.01
TRH	<0.0005	<0.01	<0.01

Results:

The mean (±SD) clearance and T½ values for endogenous GnRH and triptorelin are included in Table 26.

Table 26.

	t½ (min)	Cl (ml/min)
Endogenous GnRH	8.2 ± 1.2	1538 ± 88
Triptorelin	20.0 ± 2.5	474 ± 32

Reviewer Comments:

1. The formulation used herein was not presented. However, it is unlikely that the formulation used in this study is the to-be-marketed formulation.

2. Triptorelin clearance is significantly greater than that of endogenous GnRH.

XIII. Attachment 3: Individual Pharmacodynamic Study Review

APPEARS THIS WAY
ON ORIGINAL

Study Number: 914C127R

Title: A Phase I/II Comparative Pharmacodynamic Study of DES and Sustained Release Decapeptyl™

Objectives: To determine the hormonal response (testosterone) following the administration of Decapeptyl™ and compare to that obtained using diethylstilbesterol (DES).

Design: Randomized, open comparative study with 4 treatment arms.

Subjects: 24 patients (6 in each arm) were enrolled.

Formulation: The formulation of Decapeptyl™ used in this study was not submitted.

Dosages and Administration:

Group I: DES, 1 mg t.d.s. (orally) for 2 months.
Group II: Decapeptyl™ 1.90 mg IM q28d x 2 months
Group III: Decapeptyl™ 3.75 mg IM q28d x 2 months
Group IV: Decapeptyl™ 7.5 mg IM q28d x 2 months

Sample Collection: Blood samples were collected on Days -2 and -1 (predose), and 1-8, 10, 12, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 58 and 60 days after the initiation of the study.

Assay: The assay used to estimate the serum testosterone levels and the validation thereof were not submitted.

Results:
Pharmacodynamics

The mean serum testosterone versus time profile after administration of 1.9, 3.75 and 7.5 mg IM doses of Decapeptyl™ are depicted in Figure 6.

Figure 6.

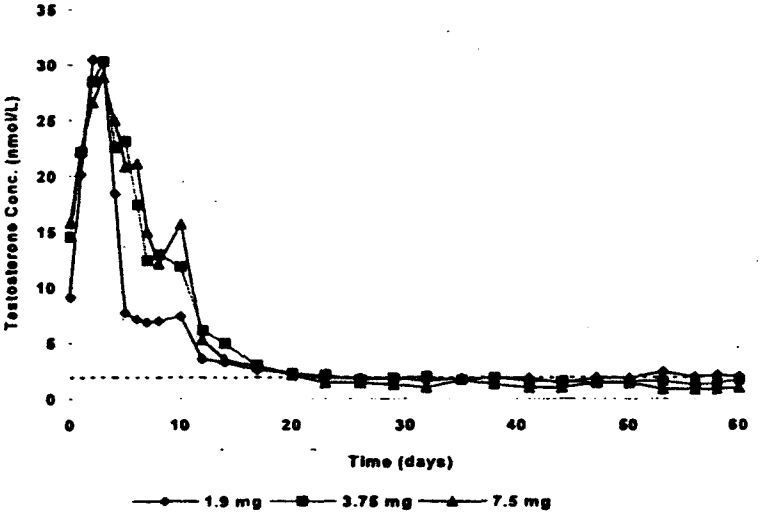


Table 27. Escape from Castrate Levels

Dose	n	# patients escaped above 2.0 nmol/L
1.9 mg	5	3
3.75 mg	5	5
7.5 mg	4	1

Sponsor's Conclusions:

1. Tumor flare following first injection, evidenced by a transient dose-independent increase in testosterone.

2. Testosterone values were suppressed the most in high-dose group (0.6-1.5 nM), intermediate in the mid-group (0.9-1.8 nM) and least in the low-dose group (0.9-2.4 nM).

Reviewer Comments:

1. Due to the small number of subjects studied herein, statistical analysis of these data is not appropriate.

2. No units are reported for the raw testosterone concentration data reported in this study. However, due to the numbers (concentrations) reported, it has been assumed by this reviewer that the units are nmol/L. Therefore, the FDA acceptable castrate level is 1.75 nmol/L.

3. Since the validation of the testosterone assay was not submitted, the confidence one can have in these data is limited.

4. All the subjects (5/5) that received the proposed to-be-marketed dose of Decapeptyl™ escaped from castrate level after Day 30 post-dose.

DRUG ABUSE AND OVERDOSAGE INFORMATION

Triptorelin pamoate the active component of Trelstar® Depot 3.75 mg is a synthetic decapeptide agonist of naturally ocurring luteinizing hormone releasing hormone. The potential for accidental or intentional abuse of Trelstar® Depot 3.75 mg is remote due to its pharmacologic properties and because it is administered under the supervision of a physician.