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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Clinical Pharmacology and Biopharmaceutics Review

MAY 18 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Submission Date:	**12/16/1999**
Related Dates	**2/11/99, 12/16/99, 2/8/00, 2/24/00, 3/30/00, 4/17/00, 4/18/00, 5/15/00**
Due Date:	**05/22/2000**
NDA:	**20715**
Drug:	Trelstar® (Decapeptyl) Depot 3.75 mg (triptorelin pamoate microgranules, lyophilized)
Sponsor:	Debio R. P.
Indication:	Palliative treatment of advanced prostate cancer
Re:	Response to the non-approval letter issued June 4, 1997
Reviewer:	Soraya Madani, Ph.D.

1 Synopsis

NDA 20-715 for Decapeptyl™, a 3.75 mg triptorelin pamoate for depot suspension, was submitted by Debio Recherche Pharmaceutique SA on June 24, 1996. The indication sought was the palliative treatment of advanced prostate cancer. On June 4, 1997 a non-approval letter was sent to Debio indicating deficiencies from clinical, biometrics, biopharmaceutics, CMC and microbiological perspectives.

Clinically the application was found non-approvable due to deficiencies in study design and conduct of the pivotal clinical trial. In addition the results of the studies indicated that an unacceptably low percentage of the patients responded to Decapeptyl®, making efficacy questionable.

In a complete response submission dated December 16, 1999, NDA 20715 was re-submitted to FDA as amendment. This submission contained a new pivotal Phase 3 study (DEB-98-TRI-01). This study is performed using the to-be-marketed formulation using monthly administration of 3.75 mg Decapeptly® for 9 months.

Dr. Gary Barnett the Clinical Pharmacology and Biopharmaceutics reviewer, reported the following deficiencies in the NDA application:

1) Based on the Agency's 90% confidence interval criteria, the provided data from the bioequivalence study (AUC and C_{max} of triptorelin) indicated that the proposed to-be-marketed formulation (pamoate triptorelin) was not bioequivalent to the formulations used in the pivotal clinical trials (acetate triptorelin).

2) The pharmacodynamics equivalence(maintenance and suppression of serum testosterone levels) of the to-be-marketed formulation and that of the clinically tested formulations under single-dose conditions was not found acceptable. The proposed to-be-marketed formulation exhibits a "spike' in the triptorelin concentration within 3 hours of administration. Dr. Barnett's concern was that the spike may result in secondary flares of testosterone on re-administration during the chronic use, resulting in escapes from castrate levels. Therefore, additional data under multiple-

dose conditions were needed to support the pharmacodynamic bioequivalence of Decapeptyl®.

3) The proposed dissolution testing method was not considered acceptable. Dr. Barnett concern was that the proposed paddle speed (200 rpm) may result in shearing or breaking of the microgranules rather than dissolution. The *in vitro* dissolution methodology described below was suggested to the sponsor. This method is used in the quality control of a currently approved product with a similar formulation to that proposed for Decapeptyl™:

Apparatus:	USP Type II glass (120 ml)
Medium:	0.4% polyvinyl alcohol, 0.1% polysorbate 80, and 20 mM lactic acid
Procedure:	—

Sponsor was recommended to use similar methodology as above with paddle speeds of — rpm.

Dr. Gary Barnett reviewed most of the relevant studies to this NDA in the original submission. His review dated 4/14/97 is attached. This review contains only those studies that are submitted in response to the non-approval letter. These are:

DEB-96-TRI-02	2-month PK study in prostate cancer patients
DEB-98-TRI-01	2-month PK study in advanced prostate cancer patients
DEB-96-TRI-01	9-month Phase 3 clinical studies in prostate cancer patients
DEB-95-TRI-03	PK of a single-dose IVB in renally and hepatically impaired patients

All of the above studies are reviewed here except for study DEB-95-TRI-03 that was reviewed by this reviewer as part of NDA review (the review of that study is attached at the end of this review).

With respect to *in vitro* dissolution method and specification the sponsor has included new information regarding development of the *in vitro* dissolution method justifying the original proposed method which is reviewed here as well.

For each deficiency listed in the non-approval letter, the sponsor has provided either justification or has submitted new data. Therefore, this review is prepared in the same manner, where the sponsor's response is reviewed point by point.

2 Recommendation

NDA 20715 submitted on December 16, 1999, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmaceutical Evaluation II (OCPB/DPE II). NDA 20715 is found acceptable.

/S/ 5/18/2000

Soraya Madani, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics

Division of Pharmaceutical Evaluation II

RD initialed by Ameeta Parekh, Ph.D., Team Leader /S/
FT signed by Ameeta Parekh, Ph.D., Team Leader /S/

cc:
NDA 20715
HFD-870 (M. Chen, S. Huang, A. Parekh, S. Madani)
HFD-580 (J. Best, N. Marks)
CDR (Barbara Murphy for Drug)

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3 OCPB review response to sponsor

Deficiency #1.

- ***Is there a need for a BE study?***

The sponsor has performed a Phase 3 clinical study (DEB-96-TRI-01) using the to-be-marketed formulation. Therefore, as the sponsor points out, there is no need for conducting a BE study. This makes the lack of BE issue in the previous submission a resolved issue.

Deficiency # 2.

- ***What is PK characteristics of triptorelin plasma conc. in the patients population?***
- ***What is the pharmacodynamic end point?***
- ***What is the relationship between triptorelin plasma conc. (PK) and testosterone plasma concentration (PD)?***

Testosterone concentrations are used as a pharmacodynamic end point in three studies, DEB-96-TRI-02, DEB-98-TRI-01, and DEB-96-TRI-01. The first two studies are Phase 1 and Phase 2 studies respectively carried out for 2 months while the last study is a Phase 3, efficacy trial carried out for 9 months. Study DEB-96-TRI-01 consists of two phases but it is only phase1 that includes pharmacokinetic analysis. In addition, in this study two formulation are tested, 1-month and 3-month formulations. Only the 1-month formulation is relevant to this NDA and those data are reviewed.

The formulation used in all of the studies is an IM (intramuscular) 3.75 mg pamoate triptorelin microgranules, which is the same as the to-be-marketed formulation. The subject population of all the three studies are men with severe prostate cancer with greater than 5 or 6 nmol/L (depending on the study) of testosterone plasma concentrations. Note that the castration levels are set at 1.73 nmol/L.

In all three studies the blood samples were measured and analyzed for triptorelin, testosterone, LH and FSH. For study DEB-96-TRI-02 blood samples are analyzed for pre-dose and end of dosing period only. While for studies DEB-98-TRI-01 and DEB-96-TRI-01 sampling took place at multiple time points to provide full plasma concentration versus time profiles. There were 13 patients in study DEB-98-TRI-01, and 30 patients in study DEB-96-TRI-02. Study DEB-98-TRI-01 measured the blood concentrations only up to Day 29, the day of second injection, while study DEB-96-TRI-02 measured blood concentrations up to Day 56, the end of 2-month study. The Phase 3 multiple dose study (DEB-96-TRI-01) measured triptorelin, testosterone, LH and FSH plasma concentrations in a sub group of 16 patients. They were measured on Day 1(1,2,4,6,10,24 hrs post-injection), Day 2 (48 hrs), Day 4, Day 6, Day 29 (the day of 2nd injection), Day 57 (day of 3rd injection), Day 85, Day 113, Day 141, Day 169, Day 197, and Day 225

The sponsor does not compare the PK or PD across the studies. The comparison of this reviewer indicates that with respect to pharmacokinetics of triptorelin in plasma, the values for C_{max}, $AUC_{0\text{-}28d}$ and T_{max} results were similar in the two studies (see Table 3). After the first injection on Day 0, on average triptorelin concentrations peaked after 1-2 hrs to ~ 20 ng/ml (ranging from [redacted] ng/ml). The concentrations decreased steadily up to Day 6 after which started plateauing around 1.29 ng/ml until the first day of second injection (Day 29). There was a slight flare up around Day 15 and Day 29. With respect

to testosterone plasma concentrations, the Phase 1 and Phase 3 studies also had very similar results (see Table 4).

One important objective of these studies was to find out how long the castration of testosterone lasts and whether injection of triptorelin for the subsequent months would lead to a flare up of testosterone resulting is escape from castration. The result of all these three studies indicate that after the first injection, on average, testosterone levels peaked at about 96 hours or 4 days (ranging 1-6 days) to a mean of 21 nmol/L (ranging [redacted] nmol/L) but had a steady decrease up to Day 21 when the mean value reached castration levels (1.735 nmol/L). In study DEB-96-TRI-02, 93% (28/30) of patients had testosterone levels below castration by Day 28 and 100% (30/30) reached those levels by Day 56 (end of 2-month). For study DEB-96-TRI-01 similar results were found for the first 2 months. As expected, for the subsequent injections (months 2^{nd} -9^{th}), by the end of each period, testosterone concentrations were below the castration levels for all the subjects. LH and FSH plasma concentrations followed similar pattern as testosterone. (See, Figure attachment).

Nonetheless, none of these studies adequately addressed the testosterone flare up issue. The design of the studies is such that it is not possible to detect such occurrence. Although testosterone plasma concentration profile is characterized adequately during the first month after the first injection, in the subsequent monthly injections the measurements of testosterone (as well as LH and FSH) took place only on the day of the injection (e.g. Day 29, Day 57, Day 85 etc.). Since the data indicate that the flare up occurs around 48-96 hours post-injection, measurements on the day of injection can not detect the possibility of testosterone flare up. A more informative design would have included time point measurements beyond first day of the injection to capture the secondary flare of testosterone. This issue was discussed with the Medical Officer Dr. Marks and Medical Team Leader Dr. Shames. They agree that the study design should have been optimized to capture the possibility of escape from castration. However, based on the experience with other GnRH agonists they are of the opinion that most likely the secondary flare is much smaller than the first one and is less likely to result in escape from castration and therefore it is not a concerning issue with respect to clinical efficacy.

In summary, there is no evidence for triptorelin accumulation in the plasma upon multiple dosing. Testosterone castration is achieved in all the subjects by the end of second injection (Day 56) and is maintained afterwards. The pharmacokinetics of triptorelin as well as testosterone plasma concentrations are similar across the studies submitted in the resubmission (where reported) with respect to C_{max} and T_{max}, and AUC_{0-28d}.

Deficiency # 3.

- *What is the purpose of in vitro dissolution study?*
- *Is the method proposed by the sponsor acceptable?*
- *Is the proposed in vitro dissolution specification able to discriminate between batches and therefore ensure uniformed quality between batches?*

To assure quality control, the sponsor has proposed the Dissolution Method and Specification that are outlined in Table 1.

Table 1. Comparison of FDA and Debio In Vitro Dissolution Test Method		
	Method used for FDA-approved acetate microsphere formulation (Lupron®)	Method proposed for triptorelin pamoate microgranules
Apparatus	USP Type II (120 mL)	USP Type II (500 mL)
Paddle Speed	75 rpm	200 rpm
Medium	0.4% polyvinyl alcohol, 0.1% polysorbate 80, 20 mM lactic acid	Water:methanol, 95:5
Procedure		Proposed Dissolution Specification: hr ± min: % to % release hr ± min: % to % release hr ± min % to % release

The same dissolution method and specification was proposed for this NDA during its first submission. The method was considered inappropriate by DRUDP, OCPB HFD-870 (Refer to NDA20-715 review by Dr. G. Barnette) primarily due to the high paddle speed of 200 rpm. The firm was recommended to use a method comparable to Lupron® dissolution method. Following OCPB/DPEII recommendation, sponsor reported that: using the Lupron®-FDA-approved method for triptorelin pamoate microgranules, sink conditions were achieved, but triptorelin was not stable in the dissolution medium. During the dissolution, the triptorelin microgranules stayed at the bottom of the flask and agglomerated. At the end of the dissolution test, only about —% of the triptorelin was released into the medium, about —% remained in undissolved microgranules, and about —% of total peptide was unrecoverable, presumably due to peptide degradation. As a result, sponsor maintains the original proposed method. The two methods are summarized in the above table.

As shown in the table, after — hours, the last sampling time point, only —% of the peptide is released. In addition the plateau is not reached. The sponsor proposed the same in vitro dissolution method and specifications for NDA [redacted] which is for [redacted] During the review of NDA [redacted] the sponsor was asked to submit complete data on the development of the dissolution method and specifications. The review of the submitted data indicated that the sponsor has tested 28 development dissolutions where the effects of 13 substances were examined in the dissolution media. The results of these studies show that preservatives, antioxidants, and detergents accelerated the degradation of the peptide. The sponsor finds that the use of solvents is more appropriate. The proposed method with a media of 95%:5% methanol : water, is stable f [redacted] (Dissolution #18, section c, submitted as an amendment to NDA20715 on 2/11/99). As indicated in Figure 1 there is an initial burst followed by very slow release of the drug substance from the formulation. Yet, due to low solubility of the drug substance very low dissolution rate is maintained past first hour. The sponsor indicates that higher concentrations of methanol did not improve the solubility. It appears that the sponsor has tried many possibilities to obtain the optimal conditions for the solubility to occur while degradation is not encountered. This reviewer is convinced that change of

conditions may not improve the extent of solubility significantly and finds the in vitro dissolution method acceptable.

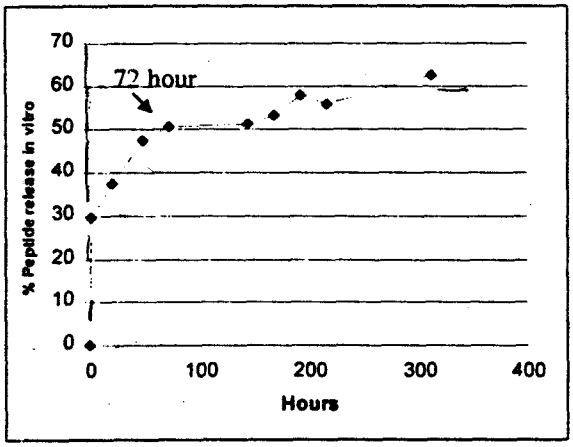


Figure 1. Mean (n=6) Dissolution of to-be-marketed formulation, ▬ 500ml, 200 rpm, 37C

To establish and justify the dissolution specifications the sponsor has chosen to use in vitro/in vivo (IVIVC) correlation approach. The in vitro dissolution profile of two batches of the drug product, one with slow in vitro release profile (D601D01K7) and one with very high values (DLGSD 95-71) were compared point-by-point with pharmacokinetic data of these batches from the clinical studies (Protocols DEB-95-TRI-02 for lot DLGSD 95-71 and DEB-98-TRI-01 for lot D601D01K7). Comparisons were carried out over a period of 35 days.

Table 2. In Vitro Dissolution Test Results for Clinical Lots

		Percent Peptide Dissolved			
Lot Number	Clinical Study (Study #)	1 hr	48 hr	72 hr	Manufacturing Method
DLGSD 95-71	Bioequivalence (DEB-95-TRI-02) ; in vitro / in vivo correlation				
D6010 2125	Prostate cancer (DEB-96-TRI-01)				
D6010 1017	Prostate cancer (DEB-96-TRI-01)				
D3312 5086	Pharmacology (DEB-96-TRI-02)				
D601D01K7	Pharmacology (DEB-98-TRI-01) ;in vitro / in vivo correlation				
Specification (±10% of in vitro / in vivo correlation lots)					

*Values obtained using latest version of the ▬ test for dissolution samples which provides a more accurate measurement of concentration but gives slightly lower values. Previously concentration of the standard was obtained ; ▬▬▬ ; this gave an underestimate due to absorption of peptide to the glass cuvette. In the revised method concentration of the standard is determined by dilutions in the ▬

However, Sponsor used an unconventional method to perform IVIVC, which is presented as a plot of time-to-release from tablet in vitro versus time-to be absorbed in vivo (Figure 2). In addition, the IVIVC plot shows an exponential characteristic that is difficult to interpret.

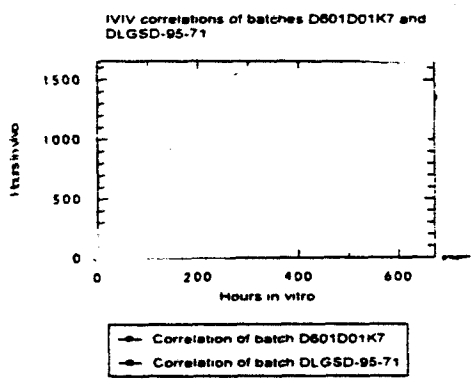


Figure 2. IVIVC correlation using clinical formulation batches (lyophilized pamoate microgranules) with slow and fast dissolution rates. The 2 clinical trials are in men with prostate cancer

This issue was communicated to the sponsor during April 1999. We asked the sponsor to assist us to understand how their IVIVC method was used to set their proposed in vitro specifications or present the data using a more conventional method; where the % absorbed from the dosage form in vivo is correlated with the % release from the dosage form in vitro. In a response-package sent on July 22, 1999, the sponsor did not address the request and maintained that their submitted IVIVC method is more appropriate. The sponsor was reminded that the use of IVIVC is neither required and nor is necessary. Yet, the IVIVC is used by sponsor to justify the wide in vitro dissolution specifications.

Table 3 summarizes the PK (triptorelin conc.) parameters for each study that is listed in Table 2, using the to be marketed formulation. The pharmacokinetic comparison indicate that the systemic exposure of batch DLGSD95-71 from study 95-02 is about 4 fold lower that those of the remaining studies (see Table 3). Interestingly, this batch had the highest rate of in vitro dissolution compared to other batches (See Table 2) allowing for much wider specifications as proposed by the sponsor. The concern was communicated via a teleconferencing with the sponsor (April 20, 2000). Sponsor was informed that the data from batch DLGSD95-71 will not be accepted for this NDA because of two reasons; one, this batch is manufactured [redacted] while all other batches are [redacted] produced; two, the 4-fold difference in the systemic exposure produced by this batch as compared to others is of concern making it not acceptable.

As indicated in Table 2 only one batch, D601D01K7 has the most accurate measurements, analytically. Therefore, the sponsor was also informed that if the individual in vitro dissolution profiles are not provided to FDA in 2 weeks, the biopharm and chemistry reviewer are going to set the dissolution specs based on the mean of the most accurately measured batch.

Triptorelin

Table 3. Pharmacokinetics of triptorelin across four PK studies in human

Study	C_{max} (ng/ml)	AUC (h*ng/ml)	T_{max} (h)	Batch #
DEB-95-TRI-02 mean ± SD **(28 days)**	**28.43 ± 7.31**	**223.15 ± 46.96**	**1.0** [redacted]	DLGSD95-71
DEB-96-TRI-02 (phase 2)	N/A	N/A	N/A	D33125086
DEB-96-TRI-01 (Phase 3) Geo mean (range) days 169-253 (84 days)	**21.3** ([redacted])	2374.7 [redacted]	**2** [redacted]	D60101017 D60102125

28 days		**791.56 (**		
DEB-98-TRI-01 (Phase 1) mean ± SD Geo mean (range) (0-672 hrs, **28 days**)	 **25.65 ±11.79** **23.21 (**	 **981.9 ± 515.22** **860.9**	 **2.5 (** **2 (**	D601D01K7

Testosterone

Table 4. Pharmacokinetics of testosterone across four studies in human

Study	C_{max} (nmol/L)	AUC (h*nmol/L)	T_{max} (h)	Batch #
DEB-95-TRI-02 mean ± SD	?	?	?	DLGSD95-71
DEB-96-TRI-02 (phase 2)	23 ± 7	Apdx16.2.6 (not found)		D33125086
DEB-96-TRI-01 (Phase 3) Geo mean (range) 0-144 h	21.4 (	2489.1 (	median 96 (	D60101017 D60102125
DEB-98-TRI-01 (Phase 1) mean ± SD Geo mean (range)	19.78 ± 4.1 19.38 (	0-672 hrs (D1-29) 3822.2 ± 815 3741.9 (	62.8 ± 36.05 Median 48	D601D01K7

On May 5, 2000 sponsor submitted new dissolution specs. The new specs were reviewed by this reviewer and Dr. Lin, the Chemistry reviewer. They were changed slightly from the sponsor's new proposal. Sponsor was informed of the suggested FDA specs and agreement was reached for the sponsor to use the following in vitro dissolution release specs.

Dissolution Method

Sponsor's new proposal		FDA suggested specs	
Time (hr)	% release	Time (hr)	% release
hr			
hr			
hr			

3.1 Special population

- ***Are the pharmacokinetics characterized in the renally and hepatically impaired patients?***

- ***Is dose adjustment required in these special populations?***

Pharmacokinetics of a single IVB dose of 0.5mg triptorelin acetate in healthy male volunteers was compared with male patients having renal or liver insufficiency (DEB-95-TRI-03, Muller study). Each of the following groups had six subjects; healthy (CL_{cr} > 100 ml/min), renal deficient (I) (CL_{cr} =20-60 ml/min), renal deficient (II) ($CL_{cr} \leq 20$ ml/min) and hepatic impaired (Child A and B, $CL_{cr} \geq 80$ ml/min). The results of PK parameters are summarized in Table 2. In general, as expected with IVB there was little difference in C_{max} and T_{max}. $AUC_{0\text{-}inf}$ was 2-fold higher in both renally impaired groups and 4-fold higher in hepatically impaired group compared to healthy volunteers. This is consistent with similar magnitude of decrease in the systemic clearance and increase in terminal half-life in these groups compared to the control. Compared to healthy volunteers, renal clearance was 22-fold lower in renally deficient (II) group but 4- and 2.5-fold lower in renally deficient (I) and hepatic impaired groups, respectively.

Table. Special Population, PK, 0.5 mg IVB, (Mean ± SD)

# Subjects	C_{max} ng/mL	T_{max} hr	$AUC_{0\text{-}inf}$ h.ng/mL	MRT hr	elim. $t_{1/2}$ hr	Cl_s mL/min	V_{ss} L	elimin. urine%	Cl_{renal} mL/min	Cl_{creat} mL/min
healthy males	48.2 ± 11.8	0.08	36.1 ± 5.8	2.51 ± 0.47	2.85 ± 0.55	211.9 ± 31.6	31.5 ± 4.9	41.7 ± 12.1	90.6 ± 35.3	149.9 ± 7.3
moderate renal impair.(I)	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
severe renal impair.(II)	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
males w/liver disease	54.1 ± 5.3	0.08	131.9 ± 18.1	10.18 ± 1.49	7.65 ± 1.14	57.8 ± 8.0	35.0 ± 5.1	62.3 ± 4.5	35.9 ± 5.0	89.9 ± 15.1

One of the main purposes of the studies in the diseased population is to make the proper dose adjustment for those patients. Therefore, either the clinical trial formulation or ideally the to-be-marketed formulation (both are sustain release formulations, SR) should have been used in the Muller Study of renally and hepatically impaired patients.

Since sponsor has used an IVB (intravenous bolus) formulation, with respect to dose adjustment, it is difficult to draw any conclusion which is reflected in the label. Therefore the conclusion that no dose adjustment is needed in hepatically and renally impaired individual is a speculation on the sponsor's part.

None the less, based on the significant change in AUC and MRT values, it appears that dose adjustment may be needed in the renally and hepatically impaired patients. However, Sponsor argues that there is no need for dose adjustment based on two grounds. First, triptorelin has wide safety margin, and second the sponsor believes the prolonged elimination half-life has no practical consequences for the sustained release (SR) formulation, the clinical and the to-be-marketed formulations (absorption rate limited kinetics, i.e., flip-flop kinetics).

These arguments are not convincing for the following reasons. First, as documented by the sponsor based on the clinical data, at the recommended dose (3.75 mg/28 days) triptorelin can cause irreversible bone loss in the young female subjects. According to Dr. Price (medical officer), any drug with such adverse effects can not be considered a drug with wide safety margin. Second, since IVB and not SR formulation is used in the Muller study, the sponsor has not characterized the absorption rate constant (K_a) in the

hepatically and renally impaired population (this parameter is not characterized in the target, but otherwise healthy women either). Relative value of K_a (absorption rate constant) to K (elimination rate constant) can determine if the kinetics is absorption- or elimination-rate-limited, this information is not provided, making the sponsor's second argument only an assumption.

Two to four fold larger AUC and t1/2 in these renally and hepatically impaired individuals compared to the control, indicates that some dose adjustment may be needed. In order to determine the extent of dose adjustment, ideally this study should have been carried with the to-be-marketed formulation or with another SR. The conclusion that no dose adjustment is needed in hepatically and renally impaired individual can be a consequential speculation on the sponsor's part.

3.2 Analytical Methodology

- ***What kind of assay is used in measuring concentrations of triptorelin and testosterone?***
- ***Do the analytical methods used in the submitted NDA have adequate sensitivity? Are they validated?***

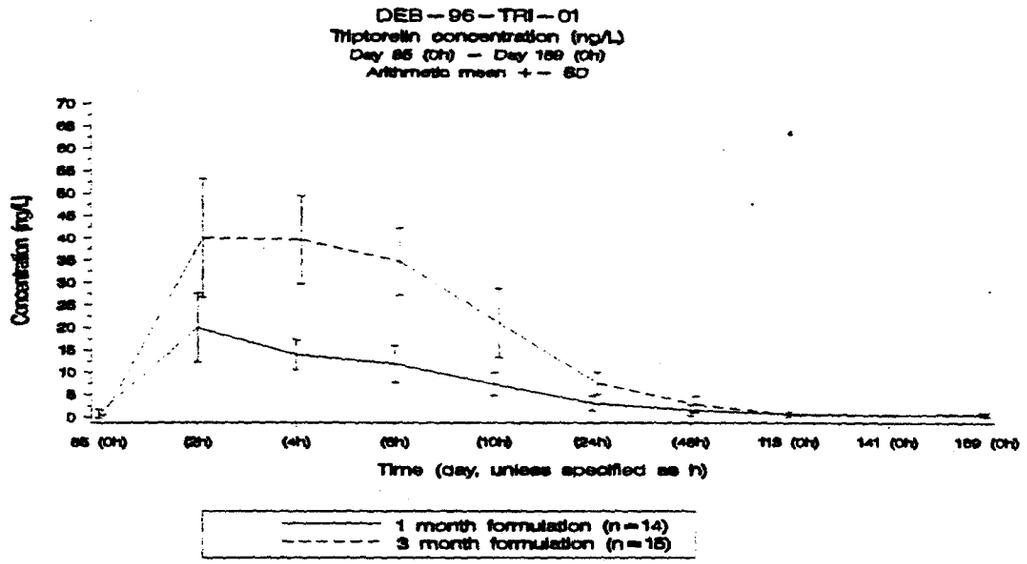
[redacted] is used for measuring both testosterone and triptorelin in human plasma. Although, the assay validation data is in human serum. The following table summarizes the details of the assay validation.

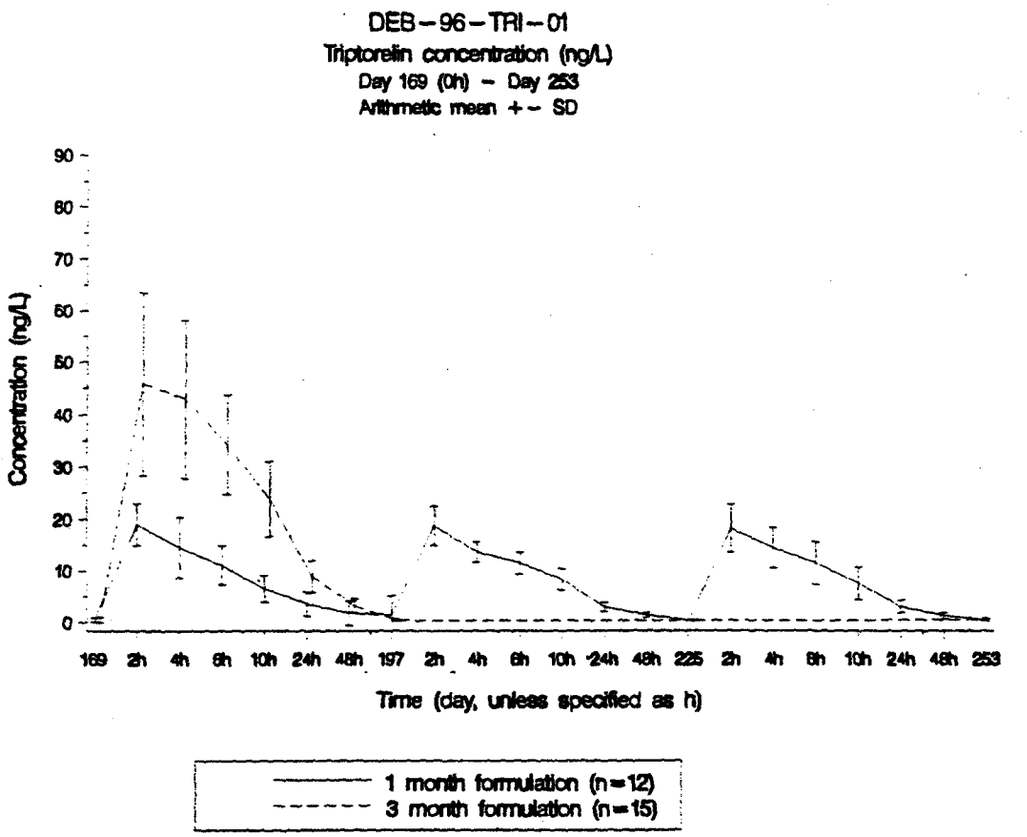
Study	Type of Biological Fluid	Method	Sensitivity of Method / Range	Specificity
DEB-96-TRI-01 DEB-96-TRI-02 DEB-98-TRI-01	Serum	[redacted]	[redacted]	[redacted]

The review of the assay data indicates adequate sensitivity and specificity of the assay. The cross reactivity is reasonably low and the assay precision and accuracy are acceptable.

Label:
Originally proposed label and FDA modified version of the Label are attached.

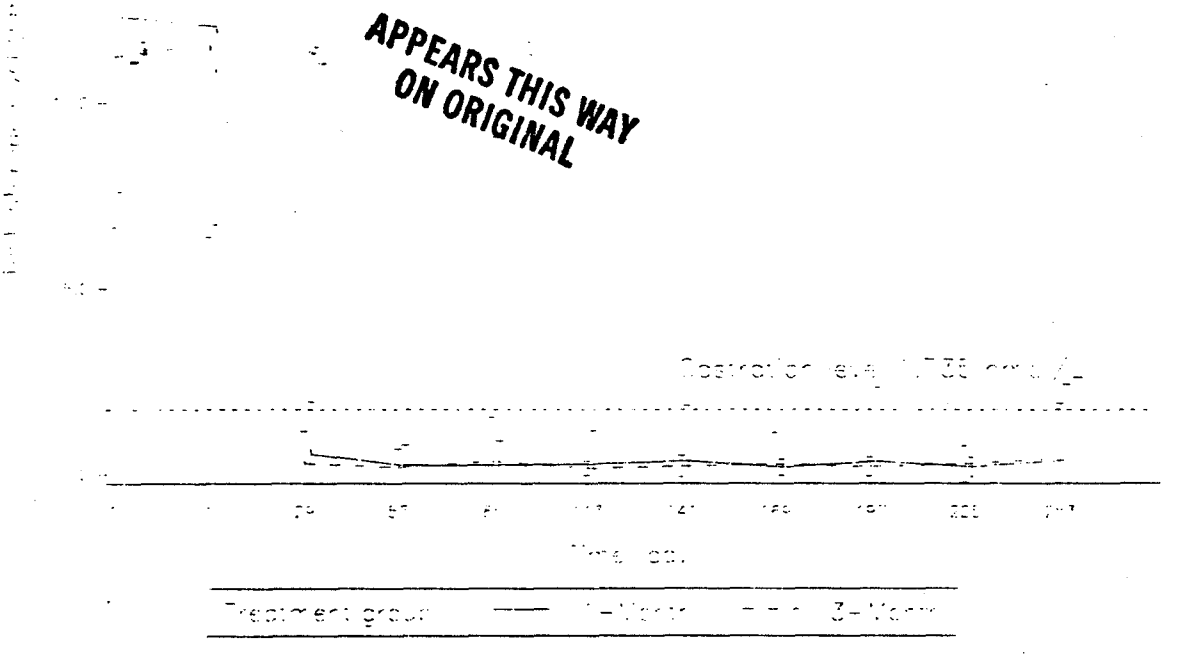
4 Figure Attachment


DEB – 96 – TRI – 01
Triptorelin concentration (ng/L)
Day 85 (0h) – Day 169 (0h)
Arithmetic mean + – SD
Concentration (ng/L)
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
85 (0h)
(2h)
(4h)
(6h)
(10h)
(24h)
(48h)
113 (0h)
141 (0h)
169 (0h)
Time (day, unless specified as h)
1 month formulation (n=14)
3 month formulation (n=15)


DEB – 96 – TRI – 01
Triptorelin concentration (ng/L)
Day 169 (0h) – Day 253
Arithmetic mean + – SD
Concentration (ng/L)
90
80
70
60
50
40
30
20
10
0
169
2h
4h
6h
10h
24h
48h
197
2h
4h
6h
10h
24h
48h
225
2h
4h
6h
10h
24h
48h
253
Time (day, unless specified as h)
1 month formulation (n=12)
3 month formulation (n=15)

DEB-96-TRI-01

Mean (± standard error of the mean) testosterone serum levels (n = 16)



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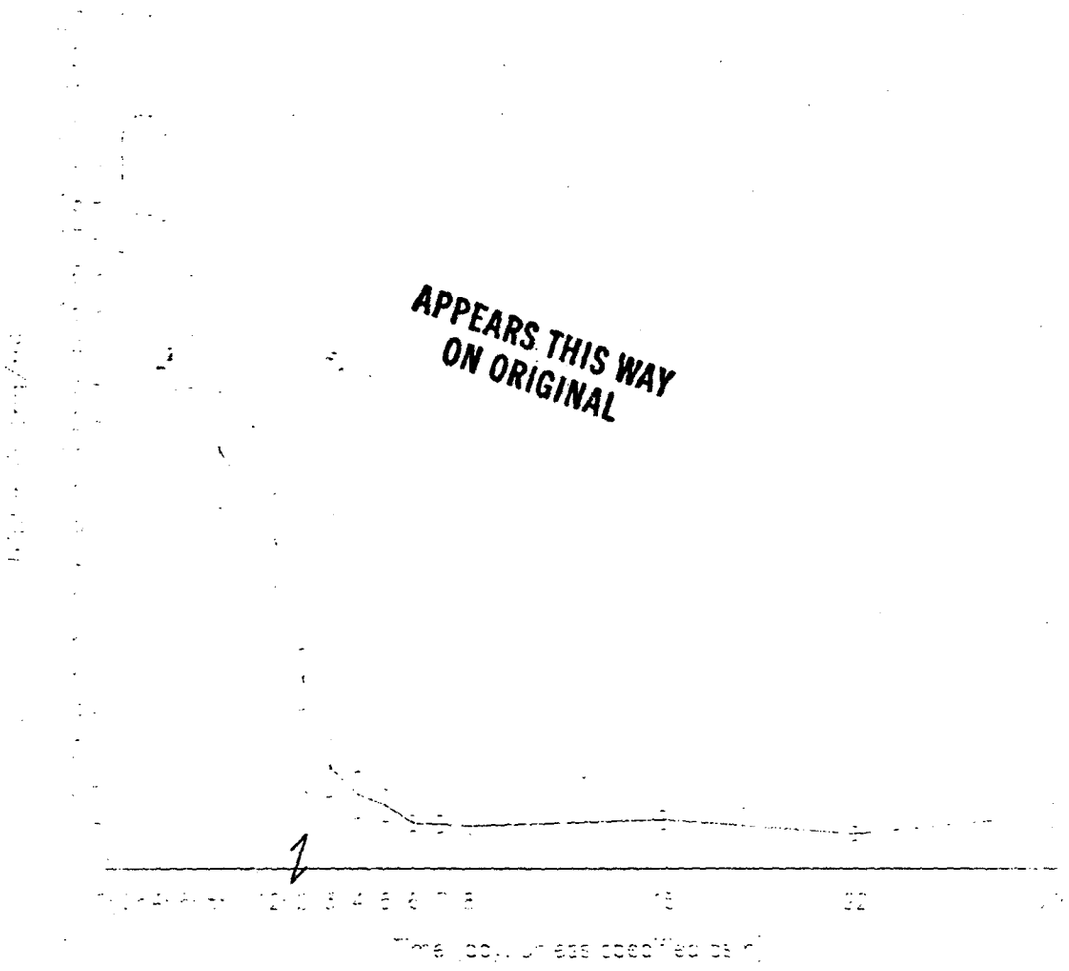
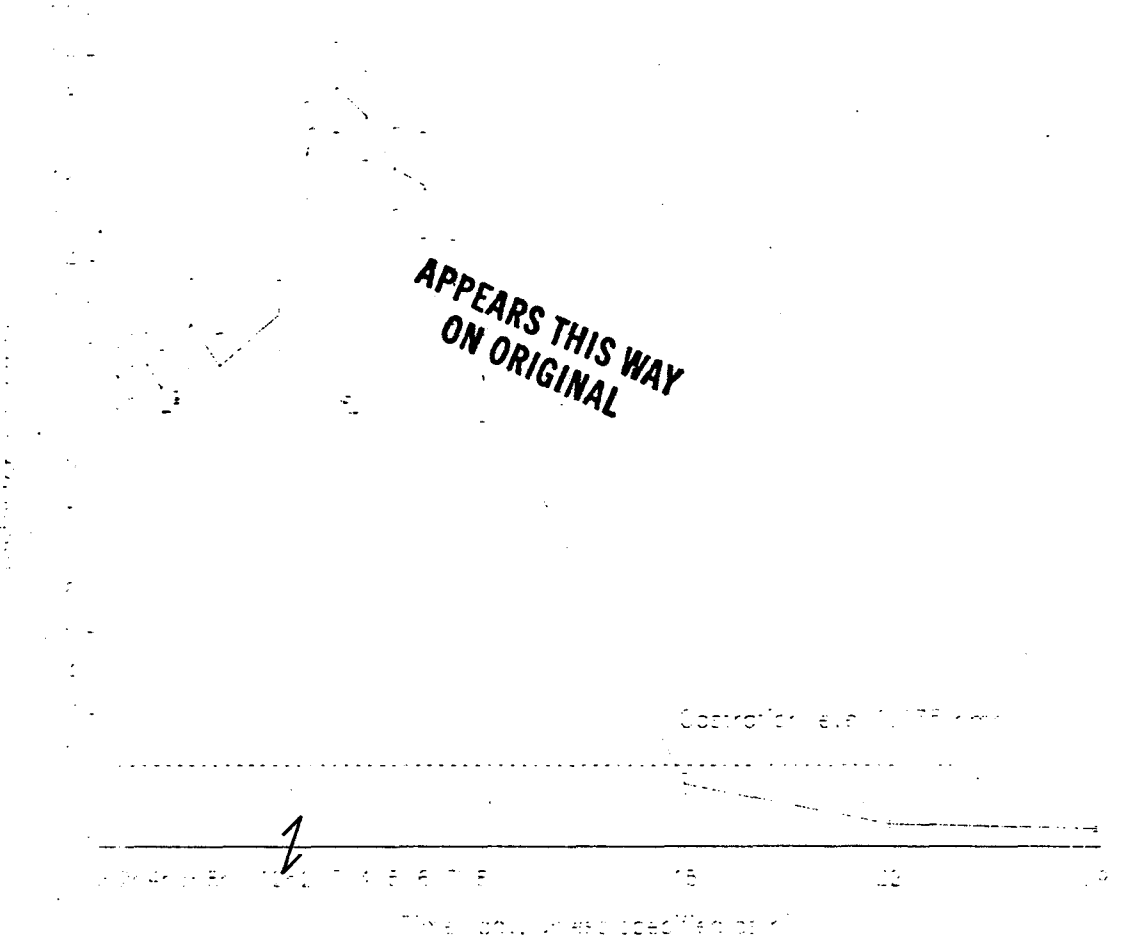
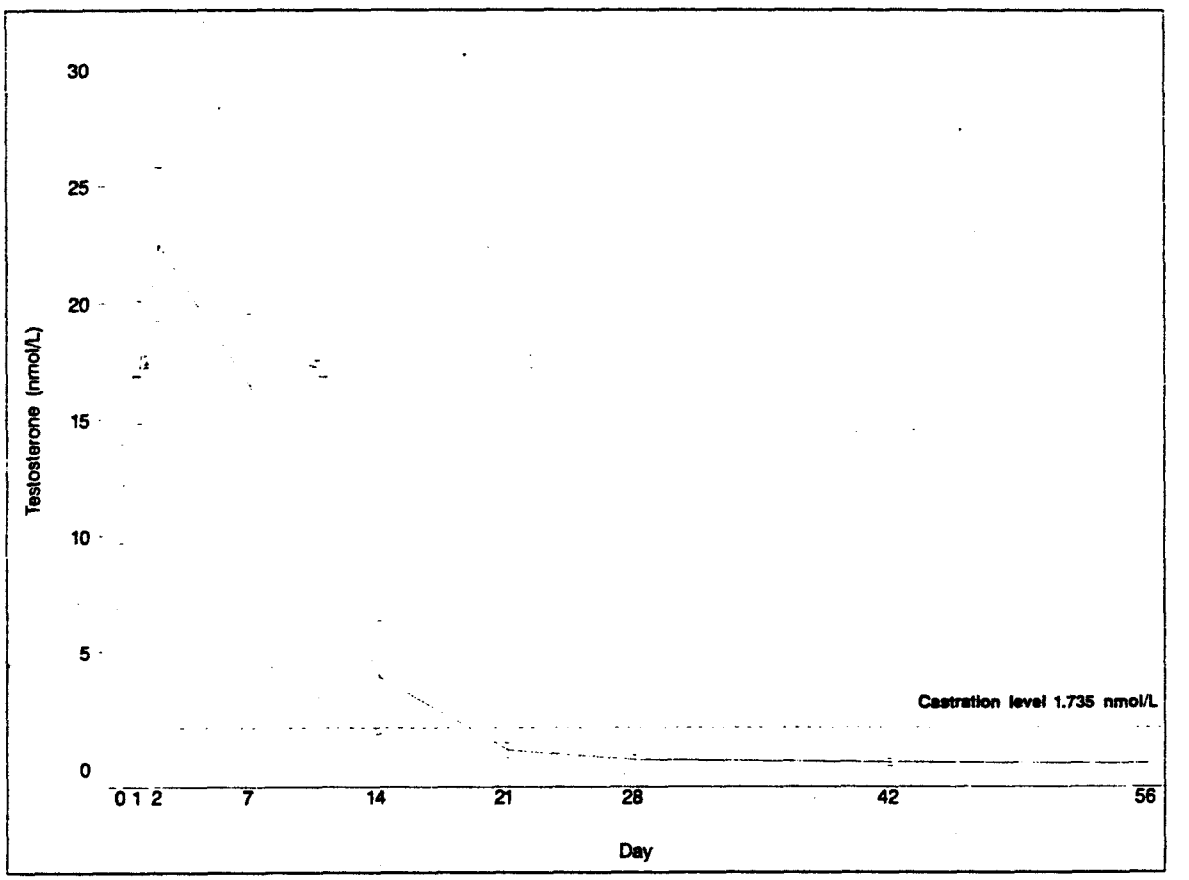
Mean (± standard error of the mean) triptorelin serum levels (n = 13)



Mean (± standard error of the mean) testosterone serum levels (n = 13)



Mean (± SD) testosterone serum



5 Study Synopsis

DEB-95-TRI-03 (Muller study) *Special population study*

- **Study title**
  Pharmacokinetic assessment of triptorelin after single intravenous bolus administration in healthy male volunteers and male patients with renal or liver insufficiency.
- **Clinical facilities**
- **Analytical facilities**
- **Principle investigator**
  Prof. F.O. Müller, MB. Ch. B.
- **Study period**
  September 1995 - March 1996.
- **Study type**
  Phase I, pharmacokinetic study.
- **Study objective**
  To assess the pharmacokinetics of triptorelin, administered as a single intravenous bolus dose of 0.5 mg triptorelin acetate in healthy male subjects and patients with varying degrees of renal or hepatic insufficiency.
- **Study design**
  Open, single-dose, non-randomized in 4 parallel groups.
- **Number of subjects**
  Group I: 6 healthy male volunteers (creatinine clearance >100 mL/min)
  Group II: 6 male patient volunteers with moderate renal insufficiency (creatinine clearance of 20 to 60 mL/min)
  Group III: 6 male patient volunteers with severe renal insufficiency (creatinine clearance < 20 mL/min)
  Group IV: 6 male patient volunteers with impaired liver function (Child A or B) and with normal renal function (creatinine clearance > 80 mL/min).
- **Test drug (IVB)**
  0.5 mg triptorelin acetate (Ferring batch#:95113).
- **Treatment duration**
  24 hours.
- **Analytical methods**
  human serum samples.
- **Criteria used for evaluation**
  Serum and urinary pharmacokinetic analysis and tolerance.
- **Results** (mean ± SD & median for T_{max})

Group	C_{max} (ng/mL)	T_{max} (hr)	AUC (h·ng/mL)	MRT (hr)	elim. $t_{1/2}$ (hr)	Cl_p (mL/min)	V_{ss} (L)	% elimin. urine	Cl_{renal} (mL/min)	Cl_{creat} (mL/min)
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
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
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
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

- **Safety information**
  No adverse events were experienced or reported by the subjects.
- **Conclusions**
  The pharmacokinetics of triptorelin can be adequately described by a 3 compartment model. The two distribution half-lives are essentially not affected by renal or hepatic insufficiency, but renal and hepatic impairment lead to a decrease in total clearance and an increase in terminal half-life. The data suggest that, whilst intact kidney and liver function are both important for the clearance of triptorelin, the liver plays a predominant role.

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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 2 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. The following *in vitro* dissolution methodology has been used in the quality control of a currently approved product with a similar formulation to that proposed for Decapeptyl™.

Apparatus: USP Type II glass (120 ml)
Medium: 0.4% polyvinyl alcohol, 0.1% polysorbate 80, and 20 mM lactic acid
Procedure: [redacted]

It is recommended that the sponsor use similar methodology as above with paddle speeds of [redacted] rpm. 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; 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.

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

/S/

RD initialed by Angelica Dorantes,Ph.D., Team Leader AD 4/14/97
FT signed by Angelica Dorantes, Ph.D., Team Leader /S/

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

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		≤ 0.1%	≤ 0.1%		
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;

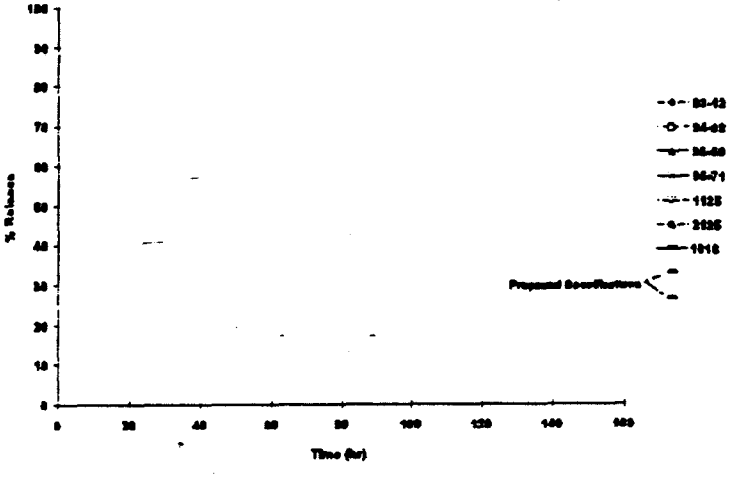
Apparatus: USP Type II (500 ml)
Medium: water:methanol (95:5)
Procedure:

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] 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] hr 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. The following in vitro dissolution methodology has been used in the quality control of a currently approved product with a similar formulation to that proposed for Decapeptyl™.

Apparatus: USP Type II glass (120 ml)
Medium: 0.4% polyvinyl alcohol, 0.1% polysorbate 80. and 20 mM lactic acid
Procedure:

It is recommended that the sponsor use similar methodology as above and properly validate, establish appropriate specifications and submit to the agency for review.

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 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

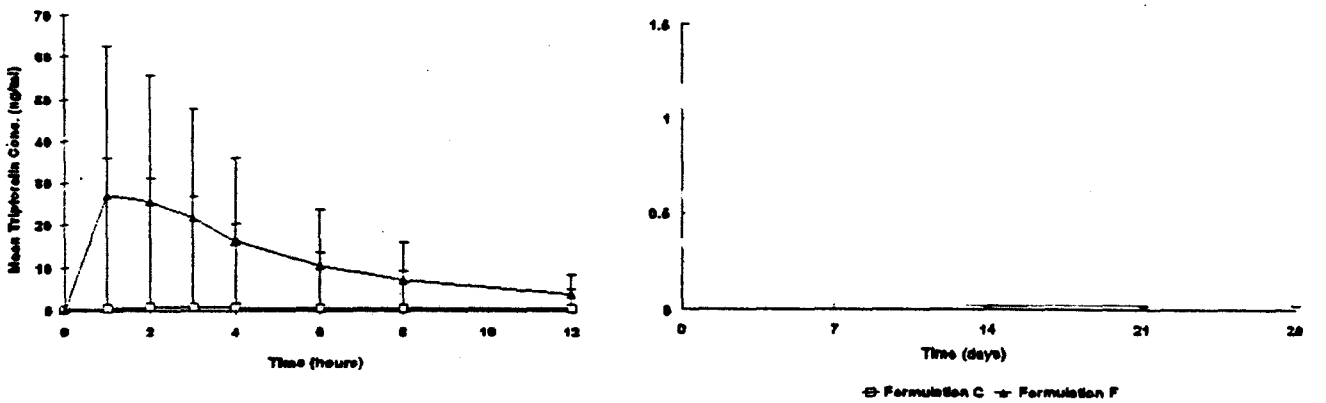
Reviewer Comment:
The 3.75 mg depot formulation used in "IVEN'S EXPERT OPINION" is NOT the to-be-marketed formulation.

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**		

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	Cmax (ng/ml)	AUC (ng*h/ml)	Tmax (h)
Formulation D	5.19 ± 2.92	190.9 ± 78.25	4 ([redacted]
Formulation F	5.87 ± 2.65	151.7 ± 64.5	4 ([redacted]
90% confidence interval	**93 - 152**	**68 - 94**	

Reviewer Comment:

1. *The to-be-marketed formulation (Formulation F) is NOT bioequivalent to the clinicaliy 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 unclear and not addressed in the submission.*

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.

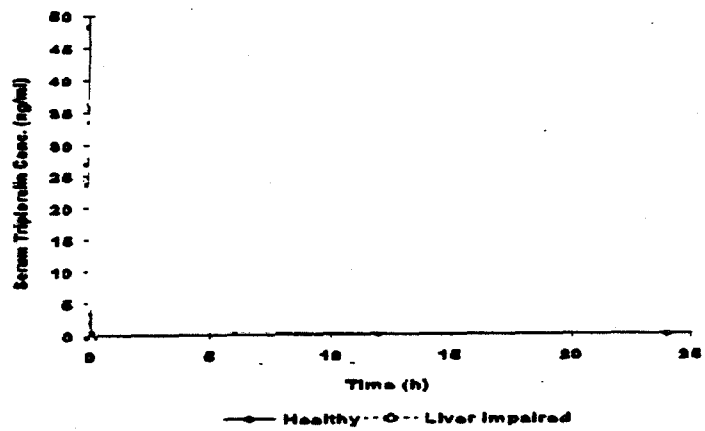
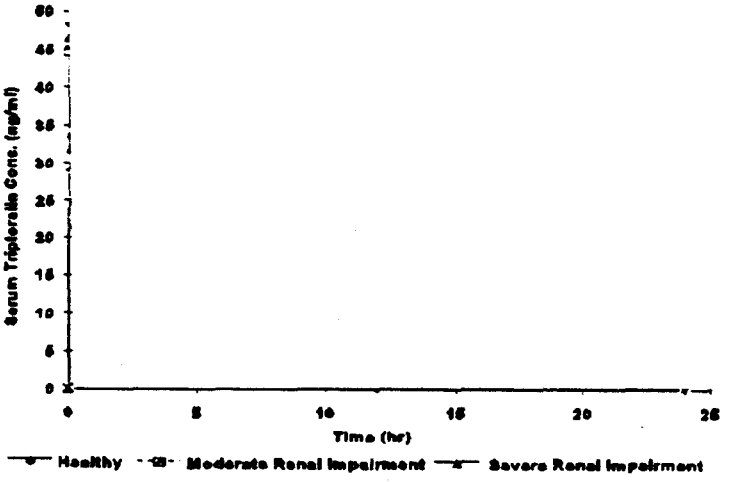


Figure 4.



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.*

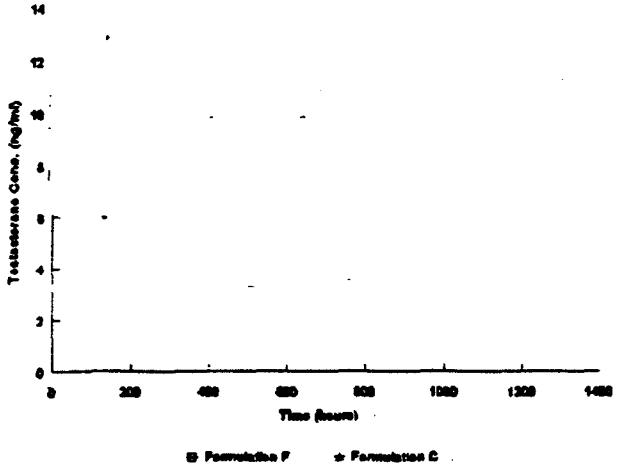
H. Drug Interactions

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.

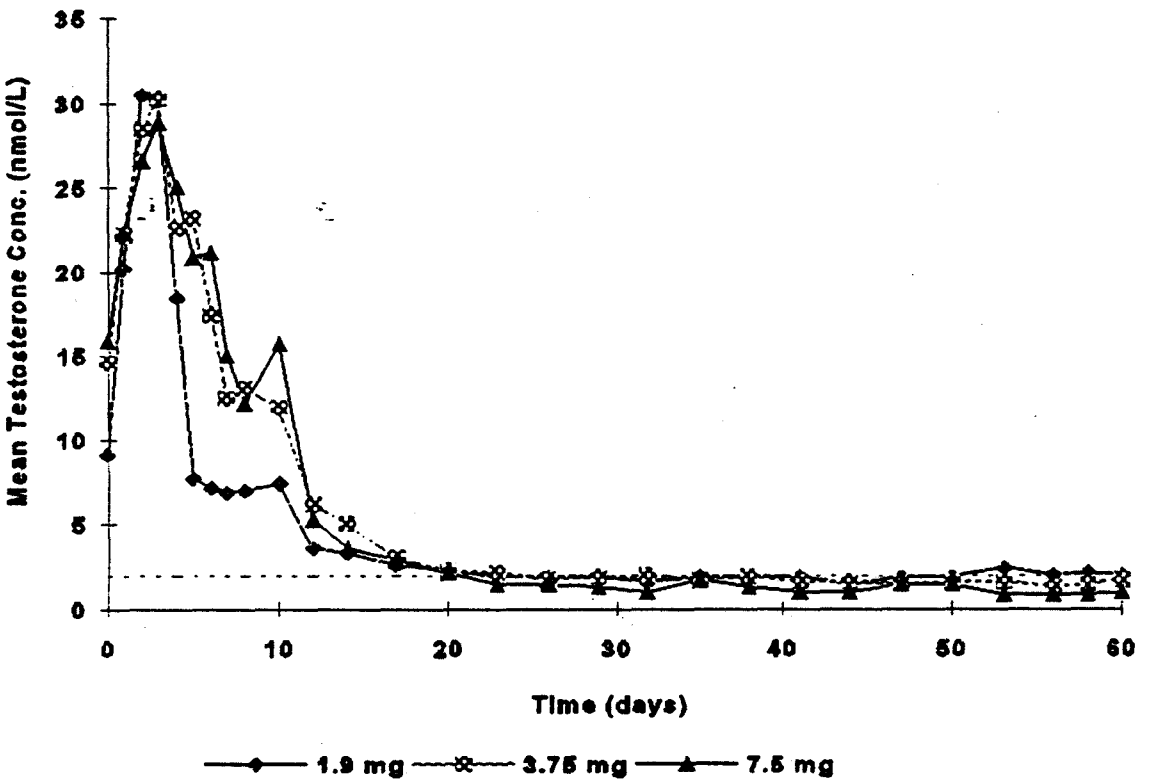


Table 11. Escape from Castrate Levels

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 [redacted] 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