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
Application Number 21-088

PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

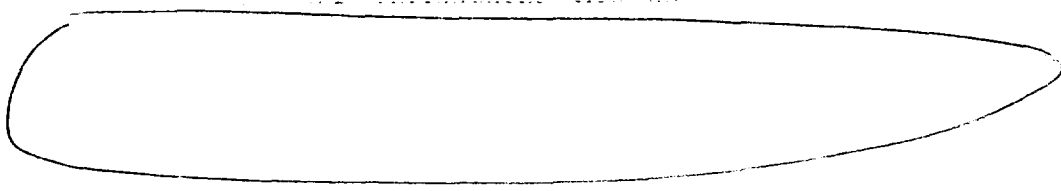
NDA: 21-088
Compound: 65 mg leuprolide acetate implant, Viadur™
 (osmotic delivery 120 µg leuprolide acetate/day/implant over 1 year)
Sponsor: Alza Corporation
Type of Submission: New Drug Product; Classification, 3S
Date of Submission: April 30, 1999; B2, July 19, 1999; SU, October 13, 1999;
 13B, December 23, 1999; BL, February 16, 2000
Reviewer: S.W. Johnny Lau, R.Ph., Ph.D.

Background

NDA 21-088 (Viadur™ 65 mg leuprolide acetate implant for palliative treatment of advanced prostate cancer; ) was submitted on April 30, 1999. Viadur™ is a single-use, titanium alloy, implantable, osmotically driven, miniaturized dosage form designed to continuously deliver leuprolide acetate at a nominal rate of 120 µg/day/implant over 1 year. The implant is inserted subcutaneously in the inner aspect of the upper arm. Viadur™ must be removed after 12 months of therapy and another implant may be immediately inserted to continue therapy. Sponsor conducted 2 clinical safety and efficacy studies (C-96-011 and C-97-010), from which clinical pharmacology and biopharmaceutics information is also assessed.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 21-088 dated April 30, 1999. OCPB/DPEII finds that the submitted information supports the "Human Pharmacokinetics and Bioavailability" section of NDA 21-088. The Clinical Pharmacology labeling comments have been communicated to and agreed by the sponsor. The following comments should be communicated to the sponsor:



Time interval (days)	Leuprolide acetate released (mg)
0 - 14	≤ 5.5
14 - 28	1.3 - 2.6
28 - 42	1.4 - 2.5

The proposed Viadur™ in vitro cumulative leuprolide acetate release rate method and specifications are acceptable on an interim basis.

2. Since the proposed in vitro release rate method and specifications only account for the release of about 10 mg of leuprolide acetate in Viadur™ implant (total = 65 mg) up to 42 days, an accelerated in vitro release rate procedure is recommended as a Phase IV commitment to investigate and account for ≥ 80% of the leuprolide acetate content in Viadur™ implant.

3. For future changes on Viadur™ drug formulation, implant components, manufacturing process, and/or manufacturing site, either an in vivo bioequivalence study or acceptable in vitro/in vivo correlations (IVIVC) should be used to support the approval of the changes. Although useful IVIVC assessments have been submitted, namely,

i) both in vitro release and estimated in vivo (humans) input rate data for leuprolide acetate for 7 days

ii) both in vitro and in vivo (humans) cumulative amount of leuprolide acetate released for 12 months

iii) both in vitro and in vivo (rats) cumulative amount of leuprolide acetate released for 3, 6, 9, and 12 months, none of the submitted data address the in vitro/in vivo relationship between 7 days and 12 months in humans. Therefore, to support future changes in Viadur™ drug formulation, implant components, manufacturing process, and/or manufacturing site, in lieu of conducting a classical in vivo bioequivalence study for 1 full year of Viadur™ administration, OCPB recommends that additional in vivo cumulative amount of leuprolide acetate released data for Viadur™ should be collected in humans at 1, 2, and 3 months to better substantiate the IVIVC. Ideally, the clinically tested batch/lot and the new-marketed batch/lot should be compared both in vitro and in vivo in this study.

/S/

27 24, 2000

S.W. Johnny Lau, R.Ph., Ph.D.
OCPB/DPEII

An optional Inter-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 21-088 was conducted on February 11, 2000. Participants included N. Marks, S. Huang, J. Hunt, A. Parekh, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader

 /S/ ? 2/24/2000

cc: NDA 21-088, HFD-870 (S. Huang, A. Parekh, J. Lau), HFD-580 (N. Marks, J. Best), CDR (B. Murphy for Drugs)

The following questions, based on the content of NDA 21-088, guided this review.

1. What is leuprolide (L)?

L is a synthetic gonadotropin-releasing hormone (GnRH) analog (nonapeptide) agonist with about 80 to 100 times the potency of GnRH and is used to treat a wide range of sex-hormone related disorders.

2. How does L work?

L primarily acts on the anterior pituitary. Administration of L causes an initial surge of luteinizing hormone (LH) from the pituitary, which increases testicular testosterone (T) production. With continued use, L causes pituitary GnRH receptors "down-regulation" and desensitization, leading to a decline in LH release and thereby suppression of T synthesis. Lowering T in the body helps to relieve pain, urinary problems, and other prostate cancer symptoms.

3. What is the proposed indication for Viadur™?

Palliative treatment of advanced prostate cancer (PTAPC).

4. What are the adverse effects of L in prostate cancer patients?

Impotence and decreased libido are universal. Hot flushes, usually mild and tolerable, occur in 35 to 71% of patients (Plosker & Brogden *Drugs* 48:930 1994). Exacerbation of symptoms (disease flare: mostly as bone pain) occurs in about 10% of patients.

5. What other L preparations are indicated for the PTAPC?

Lupron® (L acetate aqueous solution as single daily subcutaneous injection), Lupron Depot® 7.5 mg, Lupron Depot®-3 Month 22.5 mg, and Lupron Depot®-4 Month 30 mg (L acetate depot suspensions as single intramuscular injections).

6. What are the clinical safety and efficacy studies that support the approval of NDA 21-088?

NDA 21-088 contains 2 well-controlled randomized studies. Study C-96-011 is a dose-ranging study to evaluate the safety, efficacy, and repeated doses pharmacokinetics (PK) of 1 or 2 Viadur™ implants (120 or 240 µg L acetate/day; Group 1 and Group 2, respectively). Study C-97-010 is a pivotal study to evaluate the safety, efficacy and single dose PK of 1 Viadur™ implant (120 µg L acetate/day). Both studies were conducted in 2 phases (1-year Treatment Phase and then 1-year Safety Extension Phase). After the 1st phase, implants were extracted and replaced with new implants. This NDA includes data from the Treatment Phase through reinsertion for both studies and also from the 1st 2 months following reinsertion for study C-96-011. Serial serum L, T, LH, and prostate specific antigen (PSA) concentrations were quantified for the both phases of both studies.

7. What is the proposed dose for Viadur™? How is this dose determined?

One Viadur™ implant, which delivers at a nominal rate of 120 µg L acetate/day for 12 months.

Subcutaneous injection of 1-month depot suspensions containing 3.75, 7.5, or 15 mg L acetate to 22 prostate cancer patients resulted in maximum serum L concentrations of 13.09, 47.40, and 55.54 ng/mL, respectively, within 3 hours (Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989). Mean

serum L concentrations declined, reaching respective average concentrations of approximately 0.54, 0.84, and 1.10 ng/mL by Day 2. The high serum L concentration observed immediately after injection was due to a rapid and transient release of the drug from the surface of the microspheres. This was followed by a more constant release from Day 28 - Day 35; the estimated L acetate release rates were 2.89 and 4.30 µg/h (69.36 and 103.2 µg/d) following the 3.75 and 7.5 mg depot administration, respectively (Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989). Rapid increases in serum T concentrations resulted and were maintained for approximately 1 week. About 3 weeks postdose, serum T concentrations declined rapidly to castrate concentrations; there were no significant differences in these concentrations as a function of dose (Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989). Serum FSH and LH concentrations followed similar pattern.

Study C-96-011 demonstrated that 1 Viadur™ implant was as effective as 2 Viadur™ implants in suppressing serum T concentrations to castration concentrations (≤ 50 ng/dL; primary efficacy parameter). The nominal delivery rate of 120 µg L acetate/day/implant may not be the lowest effective dose for PTAPC. However, safety is not a concern at this L dose as per discussion with medical officer.

8. What are the bioanalytical methods for L, T, and LH used in NDA 21-088?

Bioanalytical assays including validation for L, T, and LH in serum samples follow (Table 1):

	L ng/mL	T ng/dL	LH mIU/mL
Method	LC-MS/MS	RIA	ICMA
LLOQ	0.1	< 3	0.04
Recovery, %	75.4	> 96	NA
Linearity	0.1 - 20	5 - 200	0.1 - 50
Accuracy, %			
intra-assay	0 - 11.7	NA	-17.3 to 2.2
inter-assay	0.11 - 1.6	4.56 - 5.81	-9.73 to -3.68
Precision, % CV			
intra-assay	1.3 - 11.6	2.94 - 7.98	7.4 ± 2.2
inter-assay	2.2 - 11.1	23.09	7.4 ± 2.3

L = leuprolide

T = testosterone

LH = luteinizing hormone

LC-MS/MS = liquid chromatography-tandem mass spectrometry

RIA = radioimmunoassay (after nonpolar solvent extraction and alumina column chromatography)

ICMA = immunochemiluminometric assay

LLOQ = lower limit of quantitation

NA = not available

Sponsor did not measure any L metabolites in studies C-96-011 and C-97-010.

9. What is the known clinical PK of L (via formulation not related to Viadur™ implant)?

Absorption

Oral L bioavailability is less than 1% (Plosker & Brogden *Drugs* 48:930 1994). Upon subcutaneous administration of 1 mg L acetate (aqueous solution) to 6 healthy men, the absolute bioavailability was 94% with a mean absorption half-life of 10 minutes and peak plasma L concentration of 32.3 ng/mL at 0.6 hours (Sennello et al. *J. Pharm. Sci.* 75:158 1986).

Following a single injection of Lupron Depot® 4 Month (30 mg L acetate suspension) in 16 orchiectomized prostate cancer patients, the mean plasma L concentration was 59.3 ng/mL at 4 hours (PDR 1999). The mean plasma L concentration from 3.5 to 16 weeks was 0.44 ± 0.20 ng/mL (range: 0.20-1.06 ng/mL). Following the onset of steady-state concentrations during week 4, L appeared to be released at a constant rate, resulting in steady plasma L concentrations throughout the 16-week dosing interval. The initial rise in plasma L and rapid decline to a steady-state concentrations is similar in the 1-, 3-, and 4-month depot formulations (PDR 1999).

Distribution

The mean steady-state volume of distribution of L following 1 mg (aqueous solution) subcutaneous and intravenous bolus administrations in healthy male volunteers was 37.1 and 26.5 liters, respectively (Sennello et al. *J. Pharm. Sci.* 75:158 1986). In vitro L human plasma proteins binding was 43 - 49% (PDR 1999).

Metabolism

Intramuscular injection of an 1-month L acetate (3.75 mg suspension) depot to a prostate cancer patient resulted in serum M-I (major metabolite; pentapeptide) concentration of 0.15 ng/mL at 1 hour and maximum serum M-I concentration of 0.86 ng/mL at 3 hours (Ueno & Matsuo *J. Chromatograph.* 566:57 1991). M-I biological activity is unknown. In another prostate cancer patient, urine M-I concentration was 1.74 ng/mL 29 days after the intramuscular depot injection. The detection limit for serum and urine M-I concentrations was 0.05 ng/mL.

M-I in 5 prostate cancer patients reached maximum concentrations 2 - 6 hours postdose (route of administration not specified) with Lupron Depot® (dosage strength and dosage form not specified) and was approximately 6% of the peak parent drug concentration (PDR 1999). One week postdose, mean plasma M-I concentrations were approximately 20% of mean L concentrations.

Elimination

In healthy male volunteers, administration of an 1 mg (aqueous solution) subcutaneous and intravenous bolus injection of L resulted in mean systemic clearances of 151 (43 S.D.) and 139 (30 S.D.) mL/min, respectively. The terminal elimination half-life for each route of administration was about 3 hours based on a two-compartment model (Sennello et al. *J. Pharm. Sci.* 75:158 1986).

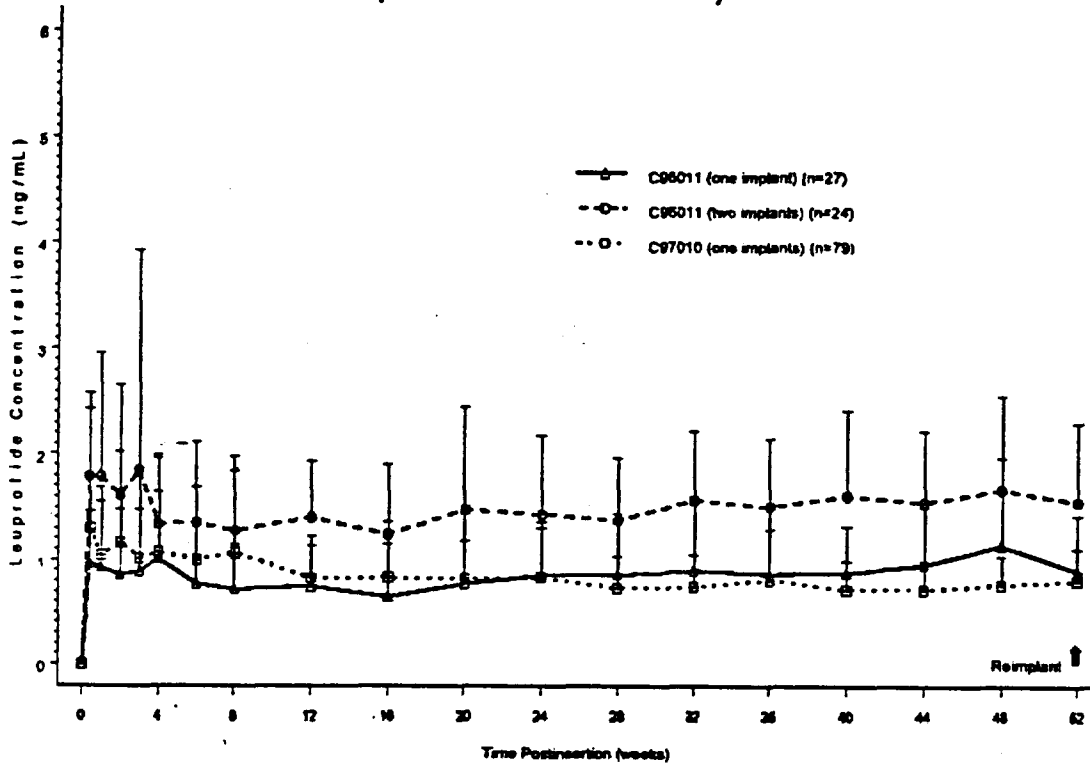
Following administration of Lupron Depot® 3.75 mg (suspension; route of administration not specified) to 3 patients (type of patients not specified), less than 5% of the dose was recovered as parent and M-I metabolite in the urine (PDR 1999).

10. What are the formulations used in the clinical studies for NDA 21-088?

The clinically-tested drug formulation is identical to the to-be-marketed drug formulation. Vendor changes to the quantitative components of the implants occurred but validated.

11. Are Viadur™ doses proportional (1 versus 2 implants)?

Figure A
Mean (SD) Serum Leuprolide Concentrations: Day 3 Through Week 52
(C-96-011 and C-97-010)



Note: C96011-two data points excluded - Patient 902 baseline and Patient 304 Week 52
C97010-excluding all data points for Patient 702, Week 52 data point for Patient
804 and baseline for Patient 702 804 806 807 812

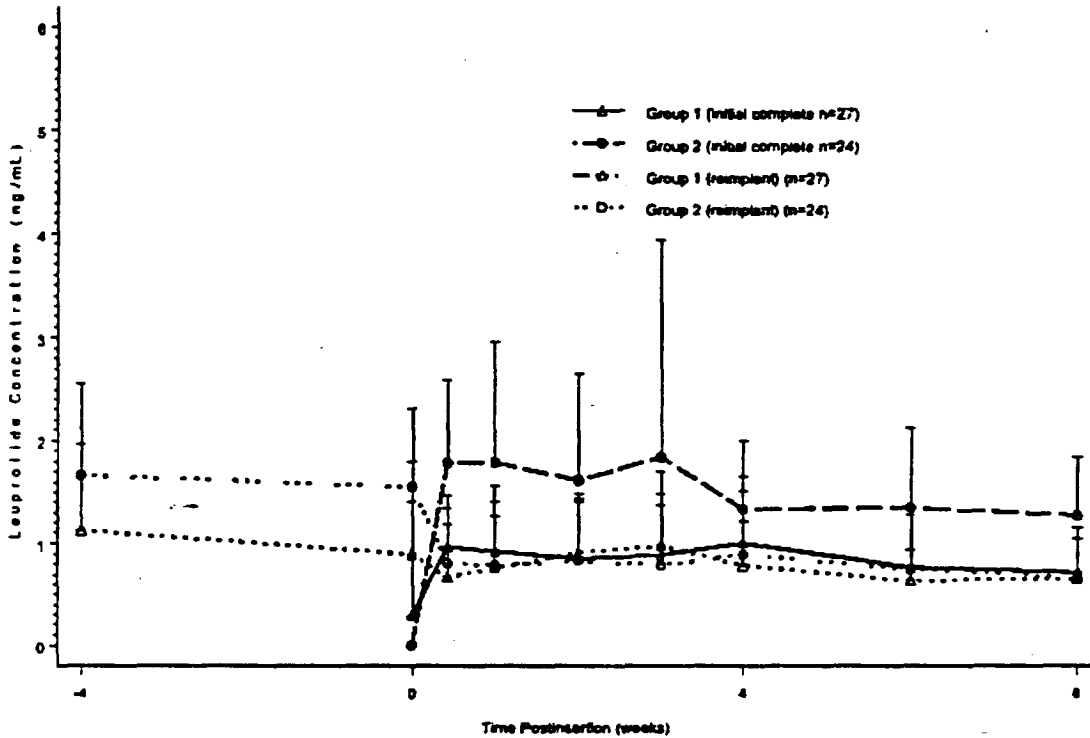
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Figure A shows the mean serum L concentrations versus time plots upon administration of 1 or 2 Viadur™ implant(s) for study C-96-011 and 1 Viadur™ implant for study C-97-010. In study C-96-011, the mean C_{avg} values following administration with 1 or 2 Viadur™ implant(s) were 0.79 ng/mL and 1.28 ng/mL, respectively. C_{avg} is the average serum L concentration maintained over the Treatment Period for an individual patient. In study C-97-010, the mean C_{avg} value following treatment with 1 Viadur™ implant was 0.93 ng/mL. The dose-normalized C_{avg} values were not significantly different between the 2 treatment groups of study C-96-011 ($p=0.09$). Thus, mean C_{avg} was proportional to the number of administered Viadur™ implant.

12. Does Viadur™ accumulate upon multiple dose administration?

Figure B

Mean (SD) Serum Leuprolide Concentrations During the Two Months After Insertion of Initial Implant(s) and During the Month Before and Two Months After Reinsertion of a New Implant (C-96-011)



Note: two data points excluded - Patient 902 baseline and Patient 304 Week 52

SOURCE: CS7010PKPDJSPKCGMMN2.BAS WITH (VER: 02/25/99 9:44)

Figure B shows the serum L concentrations versus time plots for both treatment groups of study C-96-011 (1 or 2 implants) in the following time periods:

- 2 months after the insertion of Viadur™ implant(s) in the Treatment Phase
- 1 month before and during the 2 months after insertion of the new implant in the Safety Extension Phase.

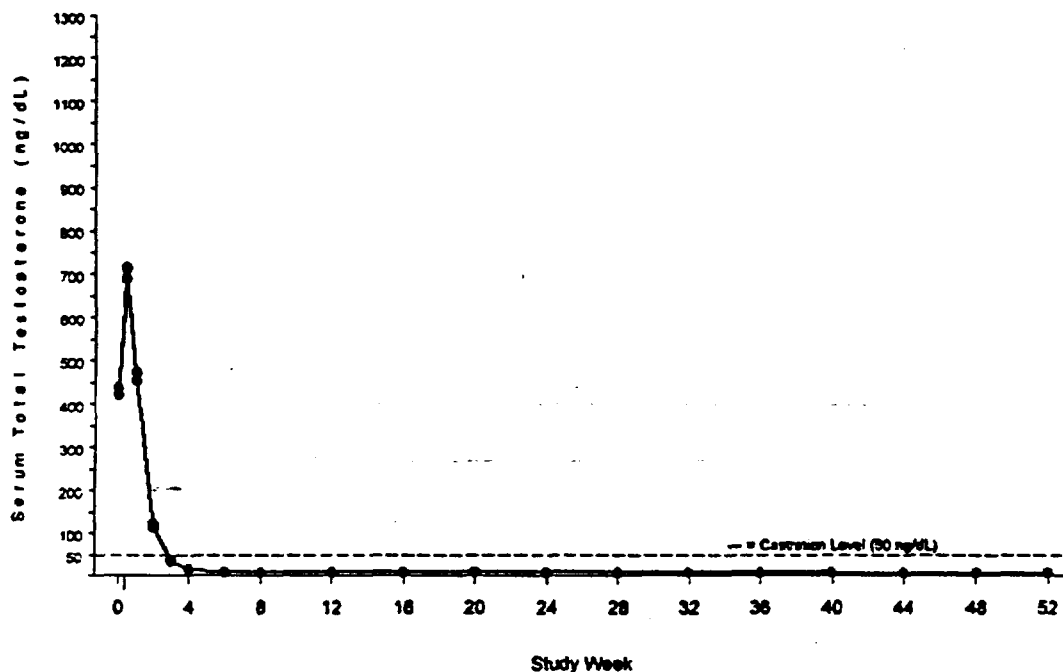
In Group 1, serum L concentrations in the first 2 months of the Treatment Phase and in the 1st 2 months of the Safety Extension Phase are superimposable. In Group 2, serum L concentrations in the 1st 2 months of the Safety Extension Phase (when these patients had 1 implant) are superimposable on the serum L concentrations measured in Group 1 patients during the 1st 2 months of the Treatment Phase. These observations suggest that there was no accumulation of L upon repeated administration, and that the serum L concentration was maintained by reimplantation.

13. What is the effect of Viadur™ on serum T concentrations?

Suppression of serum T concentrations to ≤ 50 ng/dL (castration) is the primary efficacy parameter for studies C-96-011 and C-97-010.

Figure C

Mean (+ SEM) Serum Total Testosterone Concentrations
All Patients Who Received One Implant



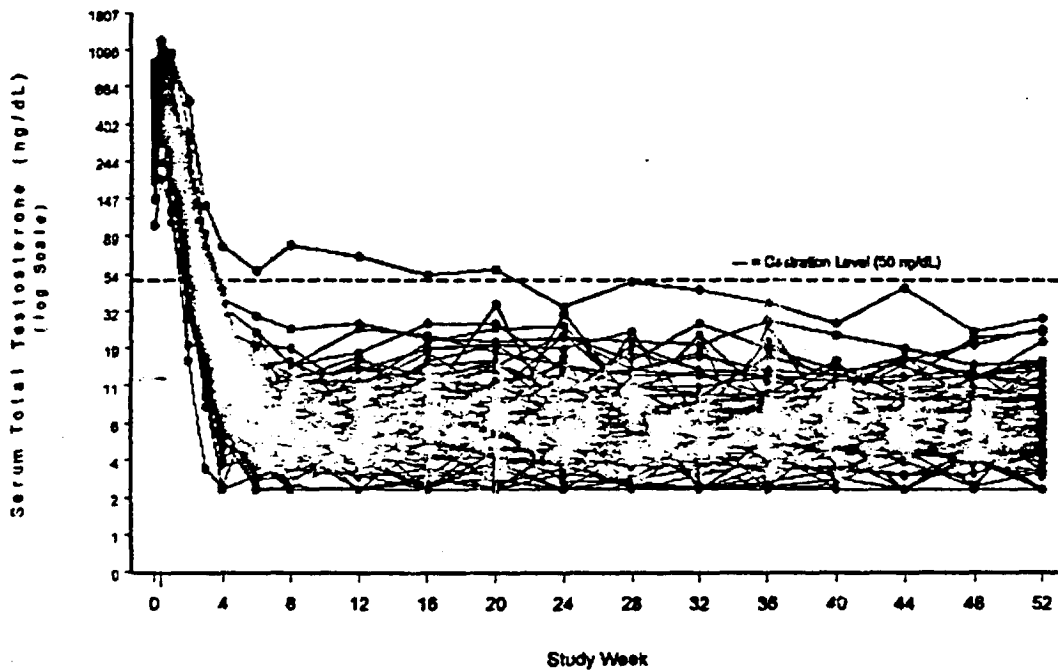
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Upon insertion of 1 Viadur™ implant, mean (\pm SD) serum T concentrations for all patients increased from 422.7 ± 161.8 ng/dL at baseline to 690.8 ± 251.9 ng/dL on Day 3 (Figure C), and then decreased rapidly, falling below the baseline mean by Week 2 (113.1 ± 91.6 ng/dL). Serum T concentrations fell below the castrate threshold between Weeks 2 and 4 in all but 1 patient (Figure D).

Figure D

**Individual Serum Total T Concentrations, Baseline through Month 12:
All Patients Treated with One Implant
(Logarithmic Scale)**



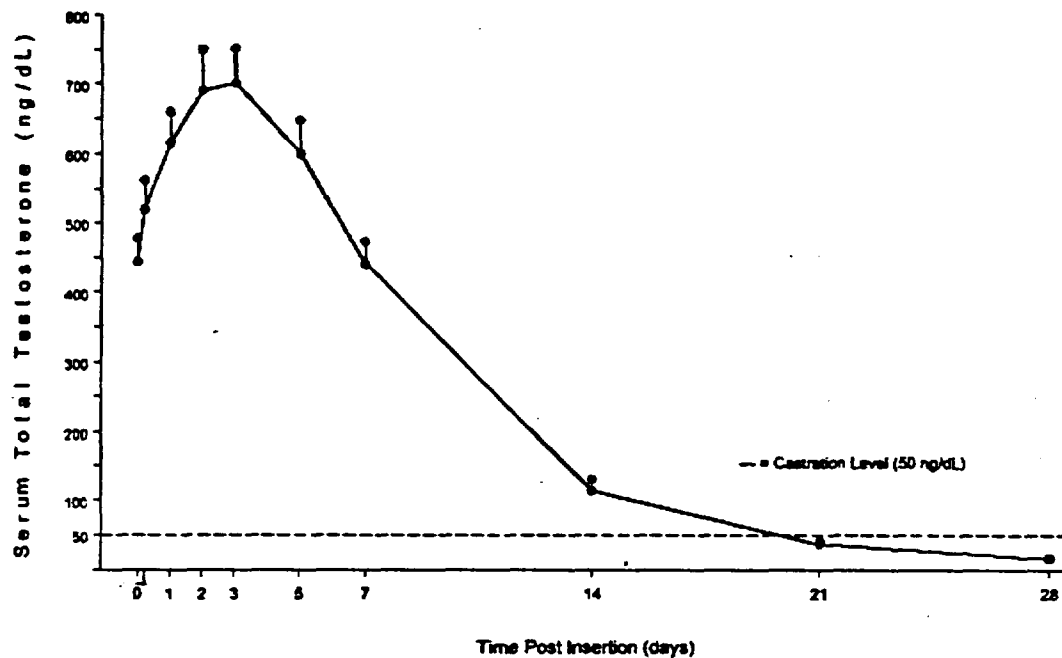
Source: CPC3A/4/02/09/STATY/GPOMT_W/008/012 (01/27/09 12:28) T_0

Once T suppression was achieved (even for the 1 patient in whom serum T was not suppressed until Week 28), T remained suppressed below the castrate threshold for the duration of the Treatment Phase (Figure D). Mean T from Weeks 6 through 52 ranged between 6.6 and 8.5 ng/dL.

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Figure E

Mean (+SEM) Serum Total T Concentrations, Baseline through Day 28:
21 Patients Included in the Special Pharmacokinetic Assessment (Study C-97-010)

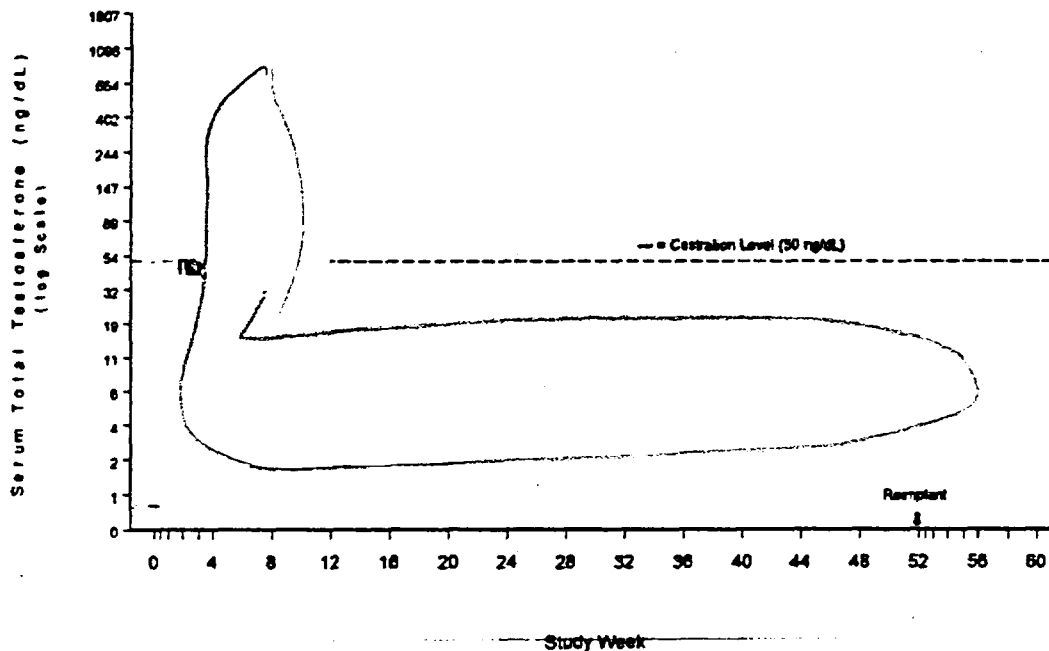


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Serum T concentrations in the 21 patients (treated with 1 Viadur™ implant) who underwent frequent blood sampling after implant insertion in Study C-97-010 showed that T rose from a baseline mean (\pm SD) of 443.1 ± 157.5 ng/dL to 519.9 ± 189.8 ng/dL at 4 hours after implant insertion (Figure E). It peaked on Day 3 (701.4 ± 222.8 ng/dL [range 370–1064 ng/dL]), then decreased, falling below the baseline mean on Day 7 (440.0 ± 153.1 ng/dL) and below the castrate threshold at Week 3 (36.8 ± 23.5 ng/dL).

Figure G

Individual Serum Total T Concentrations, One-Implant Group,
Baseline through Month 14: All Randomized and Treated Patients (Study C-96-
011)
(Logarithmic Scale)



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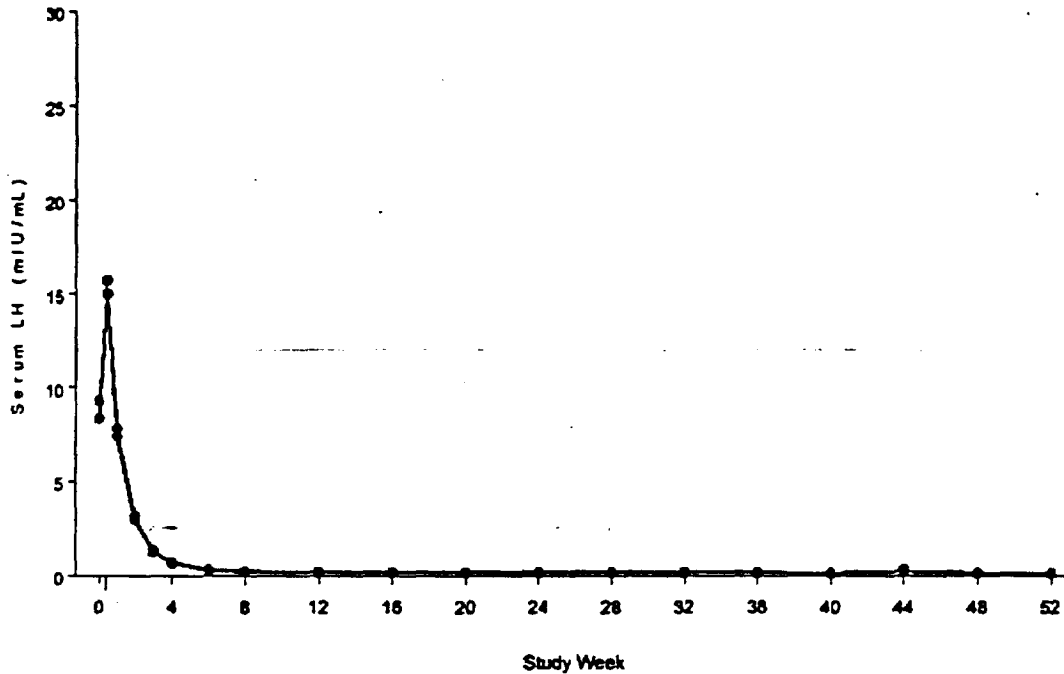
No patient in study C-96-011 had a clinically significant increase in serum T after removal of the initial Viadur™ implant and insertion of a new implant (Figure G—data for 1-implant treatment group only). Suppression of serum T was maintained in all patients throughout the 2-month follow-up period after reimplantation.

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14. What is the effect of Viadur™ on serum LH concentrations?

Figure H

Mean (+SEM) Serum Luteinizing Hormone Concentrations
All Patients Who Received One Implant

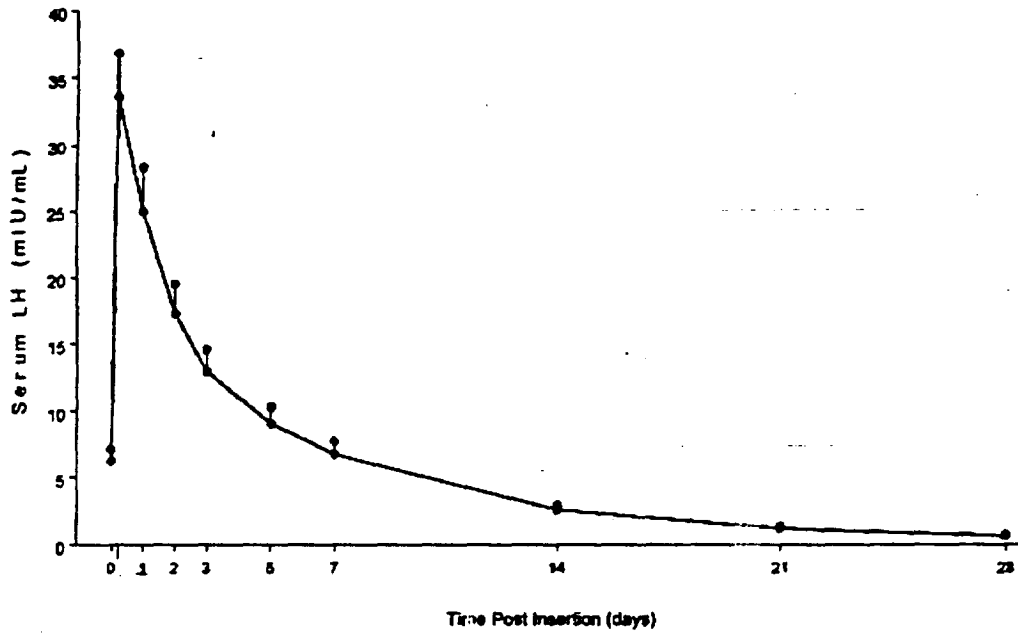


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Mean serum LH concentrations for all patients who received 1 Viadur™ implant increased from 8.37 ± 9.57 mIU/mL at baseline to 14.98 ± 7.72 mIU/mL at the 1st sampling time, Day 3 (Figure H). Mean serum LH concentrations then decreased, falling below the mean baseline concentration by Day 7 (7.45 ± 4.08 mIU/mL) and below the lower limit of the normal male range (<1.5 mIU/mL) by Week 3 (1.26 ± 0.70 mIU/mL). Once suppressed, mean serum LH concentrations remained suppressed through Week 52, ranging from Weeks 6 to 52 between 0.09 and 0.25 mIU/mL.

Figure J

Mean (+SEM) Serum LH Concentrations, Baseline through Day 28:
21 Patients Included in the Special Pharmacokinetic Assessment (Study C-97-010)



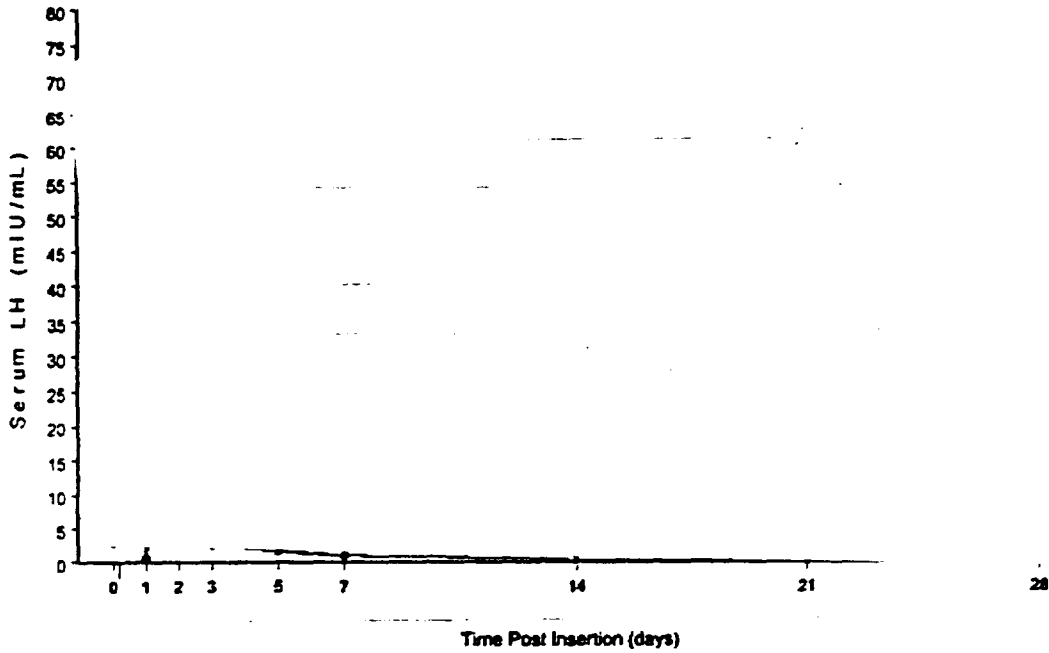
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Mean serum LH concentrations in the 21 patients who underwent frequent blood sampling after implant insertion in study C-97-010 demonstrated rapid increase in serum LH upon insertion of the Viadur™ implant (Figure J). Serum LH in these patients rose from a baseline mean (\pm SD) of 6.29 ± 3.92 mIU/mL to a peak of 33.62 ± 15.00 mIU at 4 hours after implant insertion. It then decreased, falling below the baseline mean by Week 2 (2.59 ± 1.53 mIU/mL) and below the lower limit of the normal male range by Week 3 (1.19 ± 0.65 mIU/mL).

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Figure K

**Individual Serum LH Concentrations, Baseline through Day 28:
21 Patients Included in the Special Pharmacokinetic Assessment
(Study C-97-010)**



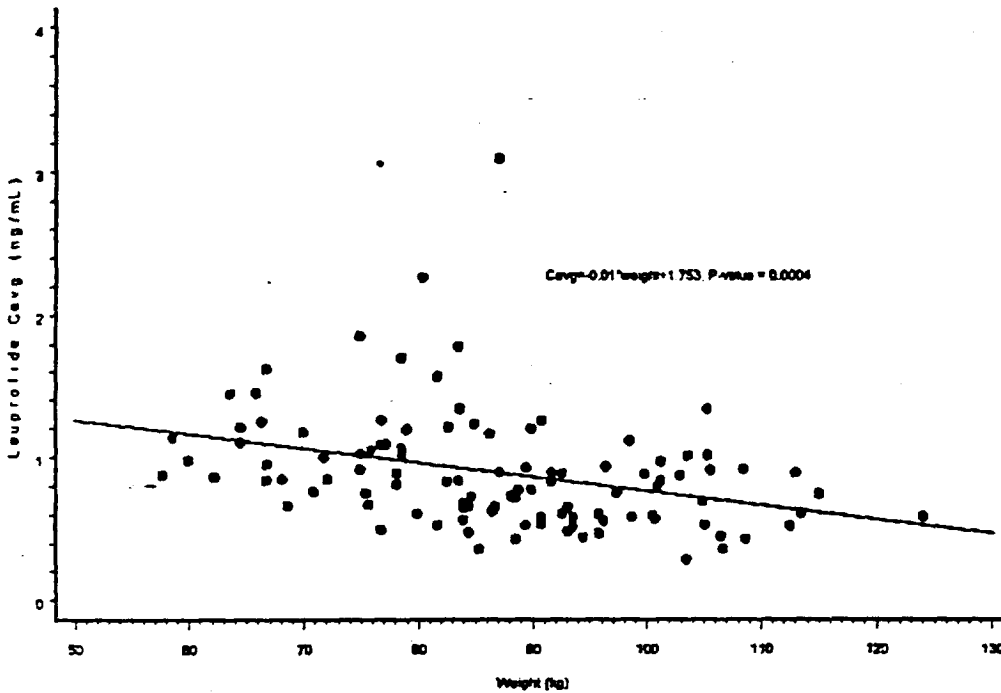
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Serum LH concentrations versus time profiles through Day 28 for the 21 individual patients in study C-97-010 are in Figure K.

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Figure M shows $L C_{avg}$ as a function of body weight. The $L C_{avg}$ values decreased with the increase in body weight ($p=0.0004$); however, all patients were effectively T suppressed. The lowest $L C_{avg}$ value (0.28 ng/mL) appeared in a patient weighing 103 kg; the $L C_{avg}$ value was 0.58 ng/mL appeared in the heaviest patient (124 kg) ($p=0.004$).

Figure M
 $L C_{avg}$ Following Single Viadur™ Implant as a Function of Body Weight



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16. What are the proposed in vitro L acetate release method and specifications for Viadur™? No standard FDA or USP in vitro dissolution method is available for implant dosage form.

The release media is 0.75% W/V Dulbecco's phosphate buffered saline + 0.2% W/V NaN_3 . Pipet 8 mL of test media solution into each labeled, sterile 15 mL conical polypropylene tubes. Weigh and record the Viadur™ systems. Warm the test tubes in a $37 \pm 0.5^\circ C$ water bath for at least 30 minutes, then carefully place the appropriate Viadur™ systems (orifice pointing up) into the test tubes via sterile tweezers and gloves. A polypropylene tube containing only 8 mL of test media solution is used as a blank. Record the start time when the systems were placed in the $37 \pm 0.5^\circ C$ water bath.

At specified sampling time points, transfer the Viadur™ systems to new labeled, sterile 15 mL conical polypropylene tubes containing fresh media that have been pre-heated to $37 \pm 0.5^\circ C$ for at least 30 minutes. To minimize any temperature change, transfer the systems swiftly via sterile tweezers and gloves. If any of the Viadur™ system accidentally falls into the $37 \pm 0.5^\circ C$ water bath,

rinse the system in an extra test tube containing fresh media before transferring to a new tube. Record transfer times when the systems were replaced into fresh media solution and any observations.

L concentrations of sampled solutions are determined via HPLC with UV detection.

The detailed in vitro release rate method and raw in vitro release data for the clinical lot are in Attachment 1.

Viadur™ L acetate implant must meet USP <724> Drug Release, Extended-Release Articles, Acceptance Table 4 - General Drug Release Standard.

The proposed in vitro cumulative release rate specifications for Viadur™ follow (Table 2):

Time interval (days)*	L acetate released (mg)
0 - 14	≤ 5.5
14 - 28	1.3 - 2.6
28 - 42	1.4 - 2.5

*The time intervals were selected to characterize the system in its initial drug release and at steady state.

17. What was sponsor's attempt on the in vitro/in vivo correlations (IVIVC) for Viadur™? Sponsor submitted 3 IVIVC approaches for Viadur™.

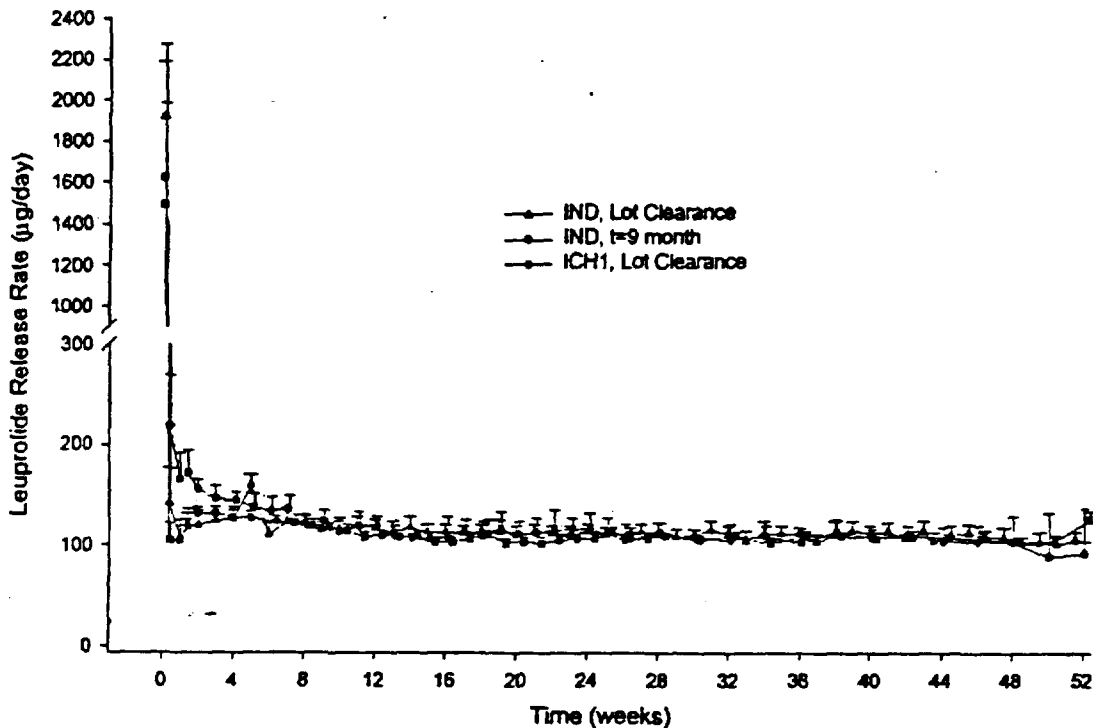
1st IVIVC approach:

The in vivo drug input rate was deconvoluted from the observed serum L concentrations following insertion of the Viadur™ L Implant in patients for Studies C-96-011 and C-97-010 via nonlinear regression. Literature L PK parameters (Sennello et al. *J. Pharm. Sci.* 75:158 1986) upon subcutaneous administration to healthy volunteers and a 2-compartment PK model with zero order input rate were used to estimate the in vivo L input rate. However, the average L clearance value (7.25 L/h) between the L clearance values upon 3.75 mg and 7.5 mg L depot subcutaneous administration to prostate cancer patients (6.9 and 7.6 L/h, respectively; Mazzei et al. *Drugs Exptl. Clin. Res.* XV:373 1989) was used in estimating the in vivo L input rate. L clearance in healthy subjects was 9.06 L/h after subcutaneous administration (Sennello et al. *J. Pharm. Sci.* 75:158 1986). All PK parameters were assumed to be same for every patient.

In Study C-96-011, the mean L in vivo input rates following treatment with Viadur™ L Implants over the 12-month Treatment Phase were estimated to be 148 µg/day in Group 1 (1 implant) and 263 µg/day in Group 2 (2 implants; 131.5 µg/day per implant). In Study C-97-010, the mean in vivo input rate was estimated to be 162 µg/day. The mean in vivo input rate for 1 implant system is about 147 µg/day (mean of 132 and 162 µg/day). Figure N shows the in vitro release rate for the lots that were used in the 2 clinical studies. The difference of about 20% between the estimated in

vivo input rate (147 $\mu\text{g}/\text{day}$) and the in vitro release rate (about 120 $\mu\text{g}/\text{day}$) may have resulted from using literature L PK parameters.

Figure N.
In Vitro Release Rate Profiles



Note: Release Rate Data in Appendix 1 and 2
Source: C97010VpkpdUSPKRR -final.jnb: Data in RR-Final.xls

In the subset of subjects in Study C-97-010 (n=21), the in vivo input rate for Days 0-1, 1-3, and 3-7 were estimated separately. Table 3 presents the mean estimated in vivo input rate in this population and the in vitro release rate at these intervals. The in vivo input rate estimates were 2 - 7% higher than the in vitro release rate.

Table 3
In Vitro Release Rate and In Vivo Input Rate during Week 1

Days	Rate ($\mu\text{g}/\text{day}$)		Ratio
	In Vitro* n=6	In Vivo n=21	
0-1	1622.6 (650.7)	1655	1.02
1-3	218.3 (51.0)	236	1.08
3-7	166.0 (24.8)	180	1.08

* Lot 1 - 0004682/871496, 9-month stability data, since systems that were implanted in these patients (Study C-97-010) were about 9 months old.

2nd IVIVC approach:

The residual L content of in vivo systems (n=71) explanted after the 12-month Treatment Phase in Study C-96-011 were analyzed. The results were compared to residual content of systems that had been used for 12 months in an in vitro release rate experiments (Table 4). In vitro residual L was 94.24% of the in vivo residual L.

TABLE 4
In Vitro versus In Vivo Residual L in Patients' Explants (One Year's Use)

	<u>Mean (SD) Leuprolide (mg)</u>	
	In Vitro	In Vivo
Initial Content	67.5 (0.9) ^a (n= 10)	
Residual	22.9 (2.4) ^c (n= 18)	24.3 (2.8) (n= 71)
Delivered ^b	44.6 ^c	43.2

^aLot clearance of Lot 1 Code/Control 0004682 / 871496

^bDelivered = Initial - Residual

^cAverage of t=1, 3, 6 month storage (25 °C) in Stability Study SS, 710

The estimated amount of in vivo L delivered (43.2 mg) corresponds to a drug release rate of about 118 µg/day. This was consistent with the in vitro release rate (Figure N). Thus, the in vivo input rate (147 µg/day) as estimated via deconvolution of plasma L concentrations (1st IVIVC approach) was overestimated and may be due to incorporation of L PK values from the literature.

3rd IVIVC approach:

Systems from 3 experimental lots were compared. L content of 10 systems was determined at the beginning of the study in each lot (time=0). Forty systems were implanted into rats for in vivo evaluation, and 40 systems were tested in vitro (37° C in phosphate buffer solution). At 4 time points (t= 3, 6, 9, and 12 months), 10 systems each from the in vitro experiment set and in vivo evaluation were assayed for residual L content.

The residual L content in systems used in these 2 studies is summarized in Table 5. The in vitro and in vivo drug release correlations were comparable between the 3 lots.

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ON ORIGINAL**

TABLE 5
Residual L Content After Delivery in Rats for Various Duration

Time (months)	Residual Leuprolide (mg)	
	In Vitro	In Vivo
Lot 2		
0	69.5 ± 1.6 (n=10)	
3	60.2 ± 1.4 (n=10)	59.3 ± 2.0 (n=9)
6	45.0 ± 1.1 (n=10)	46.8 ± 0.9 (n=10)
9	36.3 ± 1.2 (n=10)	38.0 ± 1.6 (n=9)
12	23.7 ± 1.4 (n=10)	27.0 ± 3.4 (n=9)
Lot 1		
0	68.3 ± 1.6 (n=10)	
3	55.2 ± 2.2 (n=10)	55.0 ± 1.2 (n=10)
6	43.8 ± 2.0 (n=10)	44.9 ± 3.0 (n=11)
9	32.3 ± 1.5 (n=10)	34.2 ± 1.2 (n=9)
12	23.5 ± 1.0 (n=10)	25.1 ± 2.2 (n=9)
Lot 3		
0	72.9 ± 1.9 (n=10)	
3	56.2 ± 1.5 (n=10)	54.3 ± 1.4 (n=10)
6	45.5 ± 0.8 (n=10)	43.7 ± 1.0 (n=10)
9	34.9 ± 1.2 (n=10)	34.2 ± 1.2 (n=10)
12	23.7 ± 1.0 (n=10)	24.8 ± 1.8 (n=9)

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REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Viadur, Leuprolide acetate, GnRH analog, Prostate cancer

Reviewer Name: Krishan L. Raheja

Division Name: DRUDP

HFD#: 580

Review Completion Date:

Review number: Original submission

IND/NDA number: NDA # 21-088

Serial number/date/type of submission: Original submission/4-30-1999/NDA

Information to sponsor: Yes (*) No ()

Sponsor (or agent): ALZA Corporation, Palo Alto, CA

Manufacturer for drug substance: ~~ALZA Corporation, Palo Alto, CA~~

Drug:

Code Name: CPC-2 or TDC-13

Generic Name: Duros Leuprolide Implant

Trade Name: Viadur

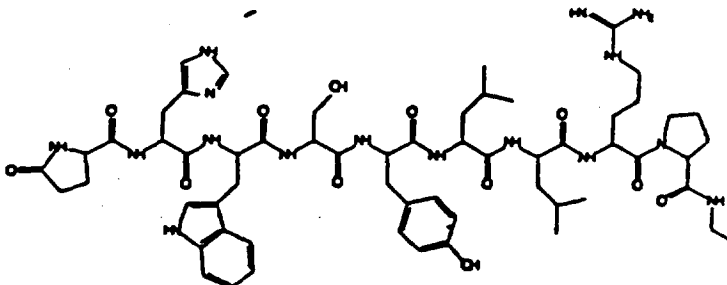
Chemical Name of drug substance: 5-Oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-Leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)

CAS Registry Number: 74381-53-6

Molecular Formula/ Molecular Weight: $C_{39}H_{54}N_{16}O_{17}/1209.1$

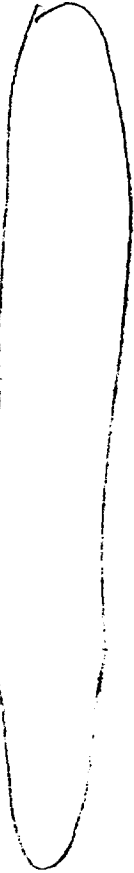
Structure:

Structural formula (free base):



pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide

DUROS Leuprolide Implant Formulation Composition

<u>DUROS Component</u>	<u>Material</u>	<u>Amount</u>
Drug formulation	Leuprolide acetate Dimethyl sulfoxide	72 mg
Osmotic engine Tablet	Sodium chloride, USP Magnesium stearate, NF Polyvinylpyrrolidone (Povidone), USP Carboxymethyl cellulose Na Sterile water for injection	
Compartment filler	Polyethylene glycol	
Reservoir	Titanium alloy,	
Membrane rate limiting	Polyurethane thermoplastic Elastomer,	
Diffusion moderator	High density polyethylene	
Piston	Thermoplastic elastomer,	
Piston lubricant	Silicone medical Fluid (SMF)	

Route of administration: The implant is inserted subcutaneously in the inner aspect of the upper arm.

Proposed clinical protocol or Use: The implant will be used for the palliative treatment of prostate cancer

Previous clinical experience with leuprolide acetate: There is an extensive clinical safety efficacy data available not only for the palliative treatment of prostate cancer, which is the indication for the DUROS Leuprolide Implant, but also for its use in the treatment of endometriosis, uterine fibroids and precocious puberty.

To establish the safety and efficacy of DUROS Leuprolide Implant, the sponsor has conducted the following 2 clinical studies with the proposed formulation:

1. A dose-ranging study evaluating the safety and efficacy of one or two DUROS Leuprolide Implants (Study C-96-011)
2. The confirmatory study evaluating the safety and efficacy of the one-implant dose (Study C-97-010).

These studies were conducted in 2 phases with a 1-year Treatment Phase followed by a 1-year Safety Extension Phase. After the first year treatment, implant(s) were extracted and replaced with a new implant. Data submitted includes the Treatment Phase through reinsertion for both studies and also from the first 2 months following reinsertion for study C-96-011.

The safety evaluation of the DUROS Leuprolide Implant led to the following conclusions:

1. The implant was well tolerated throughout the 1-year implantation period. It was also well tolerated in the 2-month after reimplantation.
2. No serious adverse effect (AE) was reported to be related to the treatment.
3. The majority of the systemic AEs were those associated with the physiologic effects of testosterone suppression.
4. Most application site reactions were secondary to the insertion or reinsertion procedures, and were mild, transient, and resolved rapidly, usually within 2 weeks of implant insertion.
5. There was no evidence of the formation of antibodies to leuprolide.

Based on data from a total of 131 patients, it was concluded that DUROS Leuprolide Implant demonstrated its safety, efficacy, and clinical utility in the palliative treatment of advanced prostate cancer.

Disclaimer -- use of sponsor's material

Introduction and drug history: Leuprolide acetate is a synthetic nonapeptide analog of the naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses 80-100 times greater potency than the native GnRH.

Daily injection and depot formulations of leuprolide acetate have been the mainstays in the hormone ablation therapy regimens since the introduction of this active substance to the market in the United States in 1985. Since then leuprolide formulations have been launched in 36 countries.

Lupron as leuprolide acetate for injection and Lupron Depot as leuprolide acetate for depot suspension are approved for various indications. Lupron injection is approved for the palliative treatment of the advanced prostate cancer and for the treatment of children with central precocious puberty. Lupron Depots 3.75 is approved for the treatment of endometriosis, Lupron Depot 7.5 mg and Lupron Depot-3 month 22.5 mg for the palliative treatment of prostate cancer, and Lupron Depot-PED 7.5, 11.25 and 15 mg for the treatment of children with central precocious puberty.

The proposed dosage form is an extension of ALZA Corporation's osmotic pump technique exemplified by the ALZET osmotic pump and the Veterinary Implantable Therapeutic System (VITS)

Clinical benefits of DUROS Leuprolide Implant: Although the safety and efficacy profiles of this product are reported to be generally comparable to those reported in the literature for the existing 1-month, 3-month, and 4-month Lupron Depot formulations, the sponsor has claimed that the DUROS Implant has the potential to provide additional benefits, including the following:

1. Maintenance of continuous therapeutic levels of serum leuprolide for one year after a single administration of the implant.
2. Minimized risk of noncompliance and thus of the disease flare.
3. Maintenance of adequate testosterone suppression for one year.
4. No observed testosterone escape during the treatment interval.
5. No "acute-on-chronic" phenomenon with the insertion of a new implant.
6. Ability to discontinue the therapy through implant removal if desired.

Based on the above suggested benefits, the sponsor implied that DUROS Leuprolide Implant represents an important advance over existing standard of care for patients with advanced prostate cancer.

Studies reviewed within this submission: Studies reviewed within this submission include sponsor's conducted chronic toxicity studies with DUROS Leuprolide Implants as well as biocompatibility studies with DUROS system components. Also biological testing, cytotoxicity testing and genotoxicity studies conducted with DUROS system components are reviewed.

Some of these studies have been reviewed

Studies not reviewed within this submission: ADME and toxicology studies for leuprolide acetate (i.e., acute toxicity, subchronic toxicity in mice, rats, dogs and monkeys; chronic toxicity in mice, rats, dogs and monkeys; carcinogenicity in mice and rats; developmental and reproductive toxicity; and genotoxicity) are not reviewed within this submission. Instead these studies have been supported by reference to TAP Holdings NDAs for Lupron (listed below) as well as to published literature for which appropriate citations and copies of publications have been provided.

TAP Holdings NDAs referred by the sponsor to support ADME and toxicology for leuprolide acetate include the following:

NDA #	Date approve	Drug name	Indications
19-010	4-9-1985	Lupron Injection	Treatment of prostate cancer
19-732	1-26-198	Lupron Depot Injection	Palliative treatment of advanced prostate cancer
20-011	10-22-1990	Lupron Depot 3.75 mg	Treatment of endometriosis
20-263	4-16-1993	Lupron Depot Pediatric kit	Treatment of children with central precocious puberty

19-943	3-30-1995	Lupron Depot Injection	Treatment of leiomyoma uteri (Uterine fibroids)
20-517	12-22-1995	Lupron Depot-4 month 30 mg	Palliative treatment of advanced prostate cancer
20-708	3-7-1997	Lupron Depot 3 month 11.25 mg	Treatment of endometriosis

PHARMACOLOGY:

Leuprolide acetate, a Gn-RH agonist, acts as a potent inhibitor of the gonadotropin secretion when given continuously in therapeutic doses. In both the animals and humans after an initial stimulation, chronic administration results in suppression of the ovarian and testicular steroidogenesis. This effect is due to the down regulation (i.e. desensitization) of the pituitary gonadotropin receptors in humans and monkeys. In the male rats, there is a direct testicular effect, resulting in the loss of the testicular LH receptors.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of leutinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in the concentrations of the gonadal steroids (testosterone and dihydrotestosterone in the males and estrone and estradiol in the premenopausal women). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. Thus in the males, testosterone is reduced to castrate levels and in the premenopausal females, estrogens are reduced to postmenopausal levels.

The decrease in the sex hormones results in the inhibition of the growth of the sex hormone dependent tumors as well as atrophy of the reproductive organs. Palliative treatment of prostate cancer is achieved by the maintenance of castrate levels of testosterone in men with prostate cancer. The effects of leuprolide acetate are reversible upon discontinuation of the drug treatment.

Mechanism of Action: Leuprolide acetate acts as an inhibitor of the gonadotropins secretion due to the gonadotropin receptor desensitization when given continuously with resultant inhibition of the gonadal steroidogenesis.

Drug Activity Related to Proposed Indication: The general effect of chronic leuprolide acetate treatment is the creation of a state of hypogonadism.

Summary of pharmacology: Both in the animals and humans, administration of leuprolide acetate results in an initial increase in the circulating levels of LH and FSH, leading to transient increase in the levels of gonadal steroids. However, continuous administration results in desensitization of pituitary gonadotropins receptors, with a decrease in the levels of LH and FSH, resulting in hypogonadism.

SAFETY PHARMACOLOGY: Referred to the FDA's approved TAP Holdings NDAs and to published literature.

PHARMACOKINETICS/TOXICOKINETICS: Referred to the FDA's approved TAP Holdings NDAs and to published literature.

The only pharmacokinetics data available with the use of DUROS Leuprolide Implant is from a 24-week toxicity study in rats (Bio-95-B025-4904) and 60-week toxicity in dogs (Bio-95-B046-4904). These studies have been reviewed

These studies are summarized below:

In the rat study, following 5 treatment groups were used:

1. Prototype DUROS Leuprolide with titanium reservoir
2. Prototype DUROS Placebo with titanium reservoir
3. Prototype DUROS Leuprolide with HDPE reservoir
4. Prototype DUROS Placebo with HDPE reservoir
5. HDPE control rod

The target dose of leuprolide was about 125 ug/day. Based on rat's body weight of 0.3 kg, the nominal leuprolide dose was calculated to be approximately 415 ug/kg/day. Serum testosterone and leuprolide levels at treatment weeks 6, 12 and 24 are shown in table below:

Table 1. Serum leuprolide and testosterone levels in rats

Group #	Testosterone (ng/dl) weeks			Leuprolide (ng/ml) weeks		
	6	12	24	6	12	24
1	3-44	5-93	44-58	2.6-33.4	0.8-15.8	2.8-5.7
2	36-368	27-143	49-206	0	0	0
3	14-84	6-64	41-132	6.4-21.0	3.3-10.1	0.3-17.1
4	30-116	49-86	43-86	0	0	0
5	34-197	40-108	40-108			

There were 14-15 male SD rats in groups 1-4 and 9 in group 5. One test and one placebo article was implanted sc in each rat. 4-6 rats were sacrificed at 6, 12 and 24 weeks post-implantation. Just prior to sacrifice blood was collected for serum testosterone and leuprolide determination.

Serum testosterone concentrations were markedly decreased in 1 of 5 DUROS leuprolide HDPE treated rats at 6 and 12 weeks and in 3 of 6 DUROS leuprolide titanium treated rats at 6 weeks postimplantation and 1 of 5 rats 12 weeks postimplantation. No decrease was seen at 24 weeks.

Serum leuprolide concentrations were very variable in both DUROS implant treated groups. There was no correlation between high serum leuprolide concentrations and low serum testosterone concentrations.

Based on these data, rat model was considered to be not an appropriate species for the investigation of testosterone suppression by leuprolide.

Table 2. Study design for 60-week dog toxicity study

Group	# of dogs	Test article	Route of Administration	# of dogs(x/x) duration in life (wks)
1	4	None	Sham surgery	(4/4) 60
2	4	Lupron Depot	Monthly IM	(4/4) 60
3	4	DUROS (aqueous formulation)	SC implant	(4/4) 22
4	6	DUROS (aqueous formulation)	SC implant	(2/6) 22 (4/6) 22 + 15 wk recovery
5	6	DUROS (DMSO formulation)	SC implant	(6/6) 60 [52 + 8 wk reimplantation]

The dose for both the Lupron Depot and DUROS formulation groups was 125 ug/day.

DUROS Leuprolide Implants provided continuous delivery of leuprolide throughout the course of the study. Groups mean serum concentrations for dogs receiving DUROS Leuprolide Implants (DMSO formulation) ranged from 0.71 to 9.63 ng/ml throughout the course of the study. However, over 86% of the group mean leuprolide concentrations was between 1.15-4.00 ng/ml. Only 3/513 (0.6%) of the analyzed samples were below the limit of quantification. A decrease in serum level of leuprolide was not observed after removal of the implants and reinsertion of new DUROS implants on Day 365.

For dogs receiving Lupron Depot, serum leuprolide concentrations ranged from below the limit of detection to 0.62 ng/ml throughout the course of the study. Of the 270 analyzed samples, 103 (38%) had concentrations below the limit of detection. Over 30% of the analyzed samples from dogs receiving 3.75 mg Lupron Depot, were below the limit of detection during the 24 hour sampling period, when leuprolide was detectable in all blood samples from dogs which received DUROS Leuprolide Implants.

Serum testosterone concentrations were decreased to castrate levels (below 50 ng/dl) by Day 29 of treatment and below the limit of quantification by Day 43 in the DUROS Leuprolide Implant (DMSO formulation) group and below the limit of detection by Day 11 in the Lupron Depot group.

Dog study results thus demonstrated that as in the rats, there was no correlation between the serum leuprolide levels and testosterone suppression.

Viadur absorption in humans: After insertion of Viadur, onset of the drug delivery was rapid, with mean leuprolide concentrations of 16.9 ng/ml at 4 hours and 2.4 ng/ml at 24 hours. Thereafter, leuprolide was released at a constant rate with mean serum leuprolide concentrations being maintained at 0.9 ng/ml (0.3-3.1 ng/ml) for one year. Upon removal and insertion of a new Viadur at 12 months, steady-state leuprolide concentrations were maintained.

In a study comparing one Viadur implant to two Viadur implants, mean serum leuprolide concentrations were reported to be proportional to dose.

It was stated that following the initial insertion, mean serum testosterone concentrations increased 50% or more by Day 3 in majority of the patients, followed by rapid decrease to baseline in all patients. Castrate levels of serum testosterone (<50 ng/dl) were achieved by 99.1% of evaluable patients between weeks 2 and 4. Once serum testosterone suppression was achieved, no escape from suppression was observed in any patient.

Leuprolide distribution, metabolism and excretion were referred to Lupron labeling.

TOXICOLOGY:

General Comments: Toxicity of leuprolide acetate has been extensively investigated and published. Leuprolide acetate has been approved by the FDA for many indications under various TAP Holdings NDAs.

Sponsor has referred all nonclinical toxicology for leuprolide acetate (i.e., acute toxicity, subchronic toxicity in mice, dogs and monkeys; chronic toxicity in mice, rats, dogs and monkeys; carcinogenicity in mice and rats; developmental and reproductive toxicity; and genotoxicity) to TAP Holdings NDAs for Lupron as well as to published literature.

Sponsor however, has conducted chronic toxicity studies with DUROS Leuprolide Implants as well as biocompatibility studies with DUROS system components. Also biological testing, cytotoxicity testing and genotoxicity studies were conducted with DUROS system components. Some of these studies have been reviewed under _____

The following toxicity studies were conducted by the sponsor:

Study Title: Evaluation of in vivo performance and local tissue response of DUROS Leuprolide in rats (32 week implantation in rats).

Study No: BIO-95-B025-4904

Vol #/page #: 1.40/6

Conducting laboratory and location: Toxicology Laboratory, ALZA Corporation, Palo Alto, CA

Date of study initiation: 7-28-1995

GLP compliance: Non-GLP

QA- Report: Yes No (*)

Methods:

Dosing:

- species/strain: rats/Sprague Dawley
- #/sex/group or time point: male
- age: adult
- weight: at least 250 g
 - satellite groups used for toxicokinetics or recovery: none
 - dosage groups in administered units: As described under ADME on page
 - route, form, volume, and infusion rate: Subcutaneous, DUROS Implants, 0.3 ul/day

Drug, lot#, radiolabel, and % purity: N/A

Formulation/vehicle: 60% propylene glycol/27% water/3% sodium carboxymethylcellulose

Observations and times:

- Clinical signs: 2 hours after implantation and then daily for 7 days
- Body weights: pre-implantation and then weekly
- Food consumption: N/A
- Ophthalmoscopy:
Hematology: weeks 6 and 12
- Clinical chemistry: weeks 6 and 12
- Gross pathology: 6, 12 and 24 weeks
Histopathology: 6, 12 and 24 weeks (implantation site)
- Toxicokinetics: 6, 12 and 24 weeks
- Other: serum testosterone at weeks 6, 12 and 24

Results:

- Clinical signs: No deaths or morbidity. HDPE reservoirs did not maintain their integrity and 3 of 4 were split at the membrane end by 6 weeks.
- Body weights: No treatment effect
- Hematology: No treatment related changes
- Clinical chemistry: No treatment related changes
- Gross pathology: as shown in table below
- Histopathology: as shown in table below
- Toxicokinetics: as given in table 1 under ADME on page

Implant site irritation was recorded both macroscopically and microscopically. Shown in table below are total macroscopic score (capsule + vascularity + fluid) and microscopic score for groups 1-5 for the 6, 12 and 24 week explants:

Table 3. Effect of leuprolide implants in rats on skin irritation

Group	Macroscopic			Microscopic		
	6 week	12 week	24 week	6 week	12 week	24 week
1	3.5	2.6	2.0	4.3	2.2	4.5
2	3.6	2.4	2.4	4.2	3.8	3.4
3	3.8	4.4	3.4	7.0	7.6	6.0
4	4.3	4.7	3.8	8.8	11.5	6.6
5	3.3	2.7	2.7	3.3	4.0	5.0

Group 1=Duros leuprolide with titanium reservoir, group 2=Duros Placebo with titanium reservoir, group 3=Duros leuprolide with HDPE reservoir, group 4=Duros Placebo with HDPE reservoir and group 5= HDPE control rod

For macroscopic evaluation, grade score scale was 0-4. Thus total macroscopic score ranged from 0-12 for capsule + vascularity + fluid. Scoring was 0-1.0 as minimal, 1.1-4.0 as mild, 4.1-7.0 as moderate, 7.1-10.0 as severe and 10.1-12.0 as extreme.

For microscopic evaluation also grade score was 0-4. Inflammation parameters checked were polymorphonuclear lymphocytes, plasma cells, macrophages, giant cells, and fibroplasia, fibrosis, necrosis and mineralization. For microscopic evaluation (test - control) scores of 1-10= mild irritation, 11-25= moderate and >26= marked irritation.

Thus macroscopic response to HDPE reservoir was mild to moderate and with titanium reservoir mild. Similar trend was seen on microscopic evaluation. Reaction was more at 12 weeks and then reduced by 24 weeks. No reaction was seen at sham sites.

As pointed out under ADME, there was no correlation between high serum leuprolide concentrations and low serum testosterone concentrations, suggesting rat not being an appropriate model for testosterone suppression by leuprolide.

Inconsistent delivery observed in the in vivo and in vitro pumping comparisons was suggested to be due to formulation stiffening, membrane protrusion and HDPE reservoir splitting. In spite of that in vivo/in vitro delivery correlated to within about 20% for implants with titanium reservoir at 6 and 12 weeks.

Overall Toxicology Summary: Both DUROS leuprolide implants with titanium and HDPE reservoirs were well tolerated. No significant macroscopic or microscopic reaction was reported at the implantation sites.

Addendum list: Copies of reviews of the original

Study title: Evaluation of in vivo performance and local tissue response of DUROS Leuprolide in dogs.

Study No. BIO-95-B046-4904

Vol #/page #: 1:40/209

Conducting laboratory and location:

Date of study initiation: 1-23-96

Date of termination: The duration of the study was originally designed to be 13 weeks.

However, because of the favorable DUROS leuprolide implant delivery results, the study was extended to 155 days for implant delivering the water/leuprolide formulation and to 60 weeks for implants delivering the DMSO/leuprolide formulation. After 52 weeks these dogs had their DUROS implants removed and replaced with new leuprolide implants from clinical production run for an additional 8 weeks.

GLP compliance: Non-GLP

QA-Report: Yes () No (*)

Methods:

Dosing:

Species/strain: Dogs/Beagle

#/sex /group or time point: as shown in table on page

age: at least 9 month

weight: N/A

satellite groups used for toxicokinetic or recovery: see table on page

dosage groups in administered units: as described under ADME. Sham operated dogs and dogs receiving injections of Lupron Depot 3.75 mg every 28 days served as controls.

route, form, volume, and infusion rate: subcutaneous, DUROS implants, 0.4 ul/day, 125 ug/day
Drug lot#, radiolabel, and % purity: N/A

Formulations: DUROS TDC-13A-40% Leuprolide acetate/60% water

DUROS TDC-13B-40% Leuprolide acetate/60% DMSO

Positive control article-Lupron Depot 3.75 mg TAP Pharmaceuticals

Observations and times:

Clinical signs: twice daily for mortality and moribundity; once daily for cageside clinical signs of toxicity, physical exam every week.

Body weight: prior to treatment and then weekly

Clinical pathology: Hamatology and clinical chemistry: Day -4 (prior to initiation), 364 and 420 (for groups 1,2, and 5 animals).

Gross pathology: All animals necropsied (groups 1, 2 and 5). All organs examined.

Organ weights: adrenal glands, brain, heart, kidneys, liver, lungs, pituitary glands, prostate gland, spleen, salivary gland, testes with epididymides, thymus and thyroid/parathyroid gland. Organ to terminal b.wt and organ/brain wt ratios calculated.

Histopathology: All required tissues preserved in 10% neutral buffered formalin.

Toxicokinetics: as under pharmacokinetics page 8 .

Results:

Mortality and clinical signs: All animals survived to scheduled termination. Compared to controls, testicles in animals of groups 2 and 5 smaller and atrophic

Body weight: no treatment-related effect

Clinical pathology: Values prior to start of study and on days 364 and 420 did not demonstrate any treatment effect.

Testosterone levels: as given under ADME on page

Leuprolide levels: as given under ADME on page

Gross pathology: At termination other than atrophy of testicles and prostate gland, no gross findings associated with the test material were reported.

Organ weights: mean weights of testes and prostate gland were significantly lower in treated groups 2 and 5 when compared to control group 1.

Histopathology: atrophy of the testes, epididymides and prostate glands.

Macroscopic evaluation of implant sites: All DUROS implants caused mild tissue reactions. DUROS leuprolide implants with aqueous formulation excised on Day 155 resulted in mild encapsulation with none to minimal increase in vascularity, and fluid accumulation. DUROS leuprolide implants containing DMSO/leuprolide formulations excised on Day 365, caused mild tissue reaction. All implant sites showed mild encapsulation and minimal increases in vascularity with no fluid accumulation. Implants excised on Day 421 (8 weeks after reimplantation), had mild to moderate encapsulation and none to minimal increases in vascularity with no fluid accumulation.

Microscopic evaluation of implant sites: Implant site reaction with DUROS leuprolide implant was mild to moderate. Five out of six implant sites from DUROS leuprolide implants with aqueous formulation, excised on Day 155 showed fibrous tissue formation associated with slight to moderate degree of fibroblastic proliferation. No histological abnormalities in sites of implants removed on Day 155 were seen after healing process on Day 286. The tissue around implants removed on Day 365 showed mild to focally severe fibrotic wall with minimal to severe inflammatory reaction luminally. The inflammatory reaction consisted of mostly histiocytes, with a mean score of 1.3 to 17.0 out of maximum site score of 56 i.e, mild to moderate reaction. Eight weeks after re-implantation on excision Day 421, there was mild to moderate compacted fibrosis surrounding a minimal to focally moderate inflammatory reaction

around the lumen. The mean inflammatory score was mild to moderate and ranged from 7.3 to 14.3 out of 56. Lupron Depot sites were not evaluated.

Leuprolide antibody assay: An enzyme-linked immunoabsorbent assay (ELISA) specific for canine IgG and IgM was used to evaluate serum samples for the presence of anti-leuprolide antibodies. For IgG, one sham dose was always positive during the 420-day study duration. Two DUROS leuprolide dogs were positive at one point. No positive values were observed for Lupron Depot treated group. For IgM, one sham treated dog exhibited positive value and none for DUROS leuprolide or Lupron Depot groups.

Summary: Serum samples from DUROS leuprolide implant or Lupron Depot treated dogs did not significantly differ from sham-treated dogs in terms of the presence of anti-leuprolide antibodies.

Study Title: An implant/explant study of DUROS implants with titanium and HDPE reservoirs in swine.

Study No. BIO-95-B026-4904

Vol #/Page #: 1.42/220

Conducting laboratory and location: 

Date of study initiation: 8-15-1995

GLP compliance: GLP

QA Report: Yes

Methods:

Dosing:

Species: miniature swine/Hanford

#/sex/group or time point: 2 females/g

Satellite groups used for toxicokinetics or recovery: groups 2 and 4 used for recovery

Dosage groups in administered units: see study design below

Route, form, volume, infusion rate: subcutaneous, DUROS Implants (titanium reservoir

Drug lot #, radiolabel, and purity: N/A

Formulation/vehicle: vehicle formulation 1% sodium carboxymethylcellulose in 0.9% saline

Experimental design: was as follows:

Table 4. Experimental design of swine toxicity study

Group No	# of pigs	# implants/pig	Duration of implantation	Euthanasia (# of wks post implantation)
1	2	6	4	4
2	2	6	4	7
3	2	6	12	12
4	2	6	12	15

Two different prototypes of DUROS implants (non-drug containing) i.e., 3 HDPE and 3 titanium DUROS implants were implanted SC in each pig. Each pig also had 2 "sham" implants. After 4 weeks, group 1 and 2 had implants removed. Pigs in group 1 were euthanized immediately, while those in group 2 were allowed to recover for 3 weeks post-explantation and then euthanized. Implants in group 3 and 4 were removed after 12 weeks and again group 3 pigs were euthanized immediately while those of group 4 were euthanized 3 weeks later.

Results: The DUROS implants were easy to implant and explant. There was minimal to moderate excapsulation of all DUROS implants. For vascularity and fluid, all sites were scored zero. Histological

examination showed a minimal response to all DUROS implants and both types of implants had a similar histological score. There was a minimal migration of the implants, ranging from none to 1 cm. The sites of the animals that were allowed to recover, healed very well. No other adverse effects were reported. Summary: Based on the above macroscopic and microscopic observations, the DUROS implants were considered very biocompatible in the swine model.

Study title: DUROS implant technology piston, diffusion moderator, reservoir, and rate-controlling membrane: 90-day subcutaneous biocompatibility study in beagle dogs.

Study No.: TR-98-5904-012.

vol.#/ page #: 1.43/1

Conducting laboratory and location:

Date of study initiation: 4-17-1998

GLP compliance: GLP

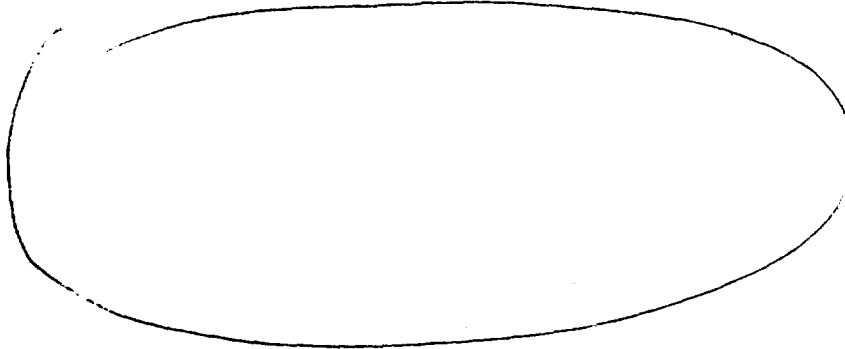
QA report: Yes

Methods:

Dosing:

Species/strain: Dog/beagle

Drug lot #



Study design: Eight dogs each received 10 dorsal, SC implants (2 each of 4 test materials and 2 USP Reference Standard Negative Control plastic strips), 5 on each side of the midline. The location of each material was randomly rotated among the 8 dogs. After 90 days of implantation, the dogs were euthanized and the local implant sites were evaluated both macroscopically and microscopically to assess local tissue reaction.

Results:

Table 5. The average severity score of tissue reactions graded as 1-5 for microscopic findings and 0-4 for macroscopic findings

Tissue reaction	Rate controlling Membrane	Piston	Diffusion moderator	Titanium reservoir	USP negative control plastic
Fibrous encapsulation	1.4	1.3	1.1	1.9	2.1
Infiltrate, mixed mononuclear	0.7	0.5	0.2	0.4	0.8
Fibroplasia, active	0.9	0.5	0.9	0.4	0.8
Infiltrate, macrophages	0.3	0.3	0.6	0.0	0.3
Infiltrate, macrophages pigmented	0.7	0.0	0.2	0.0	0.0
Hemorrhage, acute	0.1	0.0	0.0	0.0	0.0

Total macroscopic score (capsule + vascularity + fluid) for the USP Reference Standard Negative Control Plastic and the 4 implant components was 2.1 + 0.3 (mean + SD), which on the 0-12 scale presented mild reaction.

Summary: The macroscopic and microscopic scores indicated that the implanted materials were as biocompatible as the USP negative control material, because reactions of similar severity were seen in the negative control and the test material implantation sites. No evidence of infection was found in any of the sections.

Study title: USP 23: Biological testing of pellets, thermoplastic polyurethane (Tecoflex, HP-60D-20) Code number 0003074, control number 549596.

Study #: TR-96-4904-047.

Volume/page: 1.44/1

Conducting laboratory and location: _____

Date of study initiation: 6-21-1996

GLP compliance: GLP

QA report: Yes

Methods:

Dosing:

Species/strain: mice and rabbits

Sex, age and weight: N/A

Drug lot#: Tecoflex Lot No. E999-03259

Purpose of the test: USP 23 Biological tests are designed to test the suitability of plastic and polymeric materials for use in fabricating containers, for use in parenteral preparations and for use in medical devices, implants and other systems. These tests evaluate the response of animals and living animal tissue following direct contact with pieces of the test material or injection of extracts prepared from this material.

Study design: Biological response of animals to extracts of the test material was determined following single-dose injections of the extracts into mice and intracutaneous injections of the extract into rabbits. Samples of the test article were also evaluated for biological response following implantation of the material into the paravertebral muscle of rabbits for 7 days.

Tecoflex, HP-60D-20 pellets were molded into rods, annealed, irradiated and extracted in 4 different media (0.9% sodium chloride, 5% alcoholic solution in sodium chloride injection, polyethylene glycol 400 and cottonseed oil) for 72 hours at 50 °C.

In the systemic toxicity test, mice were injected with the test extract (5 mice/extract) at a dose of 50 ml/kg for sodium chloride, alcoholic solution and cottonseed oil and 10 g/kg for polyethylene glycol. The sodium chloride and alcoholic solution were injected intravenously while the polyethylene and cottonseed oil preparation by the intraperitoneal route. Mice were observed immediately after dosing and at 4, 24, 48 and 72 hours post-dosing.

In the intracutaneous toxicity in rabbits, 2 animals were used per pair of extracts. A 0.2 ml of extract of the test article was injected into 5 separate sites on the right side of the back of each rabbit, and 0.2 ml of control blank on the left side. Observations for erythema and edema were conducted at 24, 48 and 72 hours after injection. Reactions were scored on a 0-4 basis. A difference between test and control blank >1.0 was considered to be unacceptable.

Results: In the systemic injection test none of the animals treated with test material extracted in 4 extraction media showed a greater reaction than observed in the animals treated with the blanks.

In the intracutaneous injection test, none of the average scores were significantly higher (>0.5) than the average scores for the corresponding blanks. Microscopic evaluation of the implantation sites classified the material as a slight irritant when compared with the USP negative control implant.

Summary: The test article met the requirements of Class VI-50 °C plastics.

USP 23: Biological testing of water washed pellets, HDPE (Petrothene, LS6901-00) Code number 0002169, control number 539395 (study No. TR-96-4904-053) and similar testing for water washed pellets, thermoplastic elastomer (C-Flex-LS55A) code number 0002664, control number 540295 (study No. TR-96-4904-054) were conducted as for Tecoflex, HP-60D-20, described above.

Results: Test articles met the requirements for Class VI-50 °C plastics as described in the USP 23.

Study title: In vitro biological testing of Tecophilic HP-60D-20 (code No. 0003074, control No MV9720451): USP elution and MTT assay.

Study No.: TR-98-5904-016

Volume/page #: 1.44/116

Conducting laboratory and location: _____

Date of study initiation: 8-23-1996

GLP compliance: GLP

QA report: Yes

Methods:

The elution test is a qualitative cytotoxicity test designed to determine the biological reactivity of extracts of elastomeric plastics and other polymeric materials.

In the USP elution test, extracts of the test article and extracts of the positive control (latex) and negative control (USP Reference Standard Negative Control plastic) articles are added to monolayers of L-929 mouse fibroblast cells in 6-well plates. Cells are examined microscopically before treatment and then 24 and 48 hours after treatment. Cytopathic responses are assigned using USP reactivity grades ranging from None to Severe (0-4), representing responses that range from no effect to total cell lysis.

In the MTT assay, non-morphologic criteria are utilized to assess cytotoxicity. It is a spectrophotometric method for determining cell viability in culture. The cytotoxic response in the MTT assay is determined by comparing cell viability in L-929 mouse fibroblast cell cultures incubated with the test article extract or dilutions of the extract to that of cultures treated with the negative control extract.

The mitochondrial dehydrogenase-dependent reduction of the yellow tetrazolium salt, MTT, in viable cells yields a blue formazan product. After solubilization in an adequate solvent, formazan production is quantified using a scanning spectrophotometer () and relative toxicity is expressed as either the test material concentration (IC₅₀) or dilution (ID₅₀) resulting in a 50% decrease in formazan production.

Results: In the elution test, no cytopathic changes were observed except in the positive control latex extract. In the MTT assay, treatment with the test article or dilutions of the extract resulted in mean cell viability ranging from 94-98% relative to negative control cell viability.

Summary: Both in the USP elution test and the MTT assay, Tecoflex HP-60D-20 was considered non-cytotoxic.

Using the USP elution and MTT assay, it was reported that the following implant components were also not cytotoxic and as such considered to be biocompatible:

1. Pellets, Thermoplastic polyurethane (Tecoflex HP-60D-20), Code No. 0003074, Control No. 549596 (study No. TR-96-4904-049)
2. Pellets, HDPE (Petrothene LS6901-00), Code No. 0002169, Control NO. 539395 (study No. TR-96-4904-025)
3. Pellets, Thermoplastic elastomer (C-Flex LS55A), Code NO. 0002664, Control No. 540295 (study No. TR-96-4904-024)
4. C-FLEX LS55A, Code NO. 0002664, Control No. 560296 (study No. TR-96-5904-017)

Genotoxicity testing of DUROS implant components

The polymeric components of DUROS Leuprolide Implant were tested for their potential to cause genotoxicity using the following tests as outlined in the International Conference on Harmonization (ICH) of Technical requirements for Pharmaceuticals for Human use.

Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay
Chromosomal aberrations in Chinese hamster ovary (CHO) cells and
In-vivo mouse micronucleus assay

The following implant components were tested:

Extracts of Tecophilic HP-60D-20 (Code No. 0003074, Control No. MV9720451) polyurethane
Extracts of HDPE (Petrothene LS6901-00) (Code No. 0002169, Control No. 539395)
Extracts of C-Flex LS55A (Code No. 0002664, Control No. 560296)

Extraction method: Extracts of the test article were prepared using the USP guidelines of 3 cm² total surface area per ml of extractant in saline or DMSO. For extraction, test article was injection molded into "dog bone" shaped bars under conditions similar to those used for clinical parts fabrication. Bars were washed, dried, annealed, and irradiated. The "dog bones" were extracted in saline (0.9% NaCl) and PEG 400 for polyurethane and in saline and DMSO for the other two at 50 + 1.5 °C for 72 + 2 hours. Extracts of molded parts were evaluated for their genotoxic potential in either the presence or absence of mammalian microsomal enzymes. Vehicle extract controls and appropriate positive controls were included in all assays.

**Study title: Extracts of Tecophilic HP-60D-20 (Code No. 003074, Control No. MV9720451):
Salmonella-Escherichia coli/mammalian microsome reverse mutation assay with a confirmatory
assay.**

Study No.: TR-98-5904-009

Volume/page: 1.45/1

Conducting laboratory: _____

Date of study initiation/completion: 4-27-1998/9-14-98

GLP compliance: Yes

QA report: Yes

Test article lot No.: As given in study title

Study endpoint: Bacterial mutagenesis

Methodology: In this plate incorporation methodology, the S9 mix (where appropriate), the tester strain, and the test article extracts were combined in molten agar which was overlaid onto a minimal agar plate. Following incubation at 37 + 2 °C for 53 + 4 hours, revertant colonies were counted.

Strains/species/cell lines: TA98, TA100, TA1535, TA1537 and Escherichia coli strain WP2_{uvrA}.

Basis of dose selection: Cytotoxicity based on bacterial background lawn thinning or disappearance and decrease in the number of revertant colonies/plate or test article extract precipitate. The basis of high dose selection was not provided but it was stated that a minimum of 3 non-toxic dose levels was required to evaluate assay data.

Positive controls: Positive controls for respective tester strains were used and they showed at least 3-fold increase over the mean value of the vehicle (extract) control for the strain.

Criteria for a positive response: For a test article extract to be considered positive, it must produce at least 2 fold increase in the mean revertants/plate of at least one of the tester strains TA98, TA100 and WP2_{uvrA} and at least 3 fold increase for strains TA1535 and TA1537.

Doss used: The doses of the article extract were 20, 50, 100, 150 and 200 ul of extract/plate for both the saline and DMSO extracts. The cultures were dosed first with 200 ul of saline extract, mixed, then followed by the addition of 200 ul of DMSO extract so that the test system was exposed to both extracts and a total volume of 400 ul. After the initial assay, confirmatory assay was performed.

Note: Other 2 components of the DUROS implant ie., extracts of HDPE (Petrothene LS6901-00) and extracts of C-Flex LS55A were tested under study Nos. TR-98-5904-006 and TR-98-5904-003 respectively.

Note: It was reported that DMSO reacted with thermoplastic polyether urethane (polyurethane), and therefore was replaced with PGE 400 as an extraction vehicle.

Results: The test articles did not cause a positive increase in the mean number of revertants per plate with any of the tester strains either in the presence or absence of microsomal enzymes.

Study title: Extracts of Tecophilic HP-60D-20 (Code No. 0003074, Control No. MV9720451): Chromosomal aberrations in Chinese hamster ovary (CHO) cells.

Study No.: TR-98-5904-010

Volume #/page#: 1.46/1

Conducting laboratory: _____

Date of study initiation/completion: 5-14-98/2-26-99

GLP compliance: Yes

QA report: Yes

Test article lot #: as given in study title

Study endpoint: cytogenetic evaluation of chromosomal damage

Methodology: In this assay, test article extracts were prepared as described under the Ames test except that a PEG400 extract of the test article was prepared instead of a DMSO extract. CHO cells were exposed to extracts of the test material in the presence and absence of mammalian microsomal enzymes (S9 mix). At predetermined intervals after exposure, cells were arrested in metaphase with 0.1 ug/ml colcemid. Cells were then harvested, stained, and evaluated microscopically for evidence of chromosomal aberrations in chromosomes or chromatids.

Replicate cultures of CHO cells were incubated for 17.8 hours without metabolic activation or 3 hours with metabolic activation and harvested 20 hours from the initiation of treatment.

Strains/species/cell lines: CHO cells

Doses used: Cultures were dosed sequentially with 10.0, 7.5, 5.0, 2.5 and 1.0 ul/ml of PEG extract and 100, 75, 50, 25, and 10 ul/ml of sterile saline extract, respectively. The vehicle control cultures were dosed with 10 ul/ml of the sham PEG extract and 100 ul/ml of the sham sterile saline extract. A confirmatory assay was performed after the initial trial.

Assay acceptance criteria: The negative and vehicle control culture must contain less than 5% cells with aberrations. Positive control must be significantly higher ($p < 0.01$) than the vehicle controls. There should be at least 3 analyzable dose levels. If aberration results are negative and there is no significant

reduction (approx >50%) in mitotic index, the assay must include the highest applicable dose (PEG and sterile saline extracts of 10 and 100 ul/ml, respectively).

Essay evaluation criteria: 1. Percentage of cells with structural aberration
2. Percentage of cells with more than one structural aberration
3. Evidence of a dose-related increase in aberrations

Positive response: A significant increase in the number of cells with chromosomal aberrations is observed at one or more dose levels.

Negative response: no significant increase is observed in the number of cells with chromosomal aberrations for any of the dose levels.

Chromosomal aberrations in Chinese hamster ovary cells was also run for the following 2 DUROS implant components:

Extracts of HDPE (Petrothene LS6901-00) (Code No. 0002169, Control No. 539395). Study No. TR-98-5904-007

Extracts of C-Flex LS55A (Code No. 0002664, Control No. 560296). Study No. TR-98-5904-004

For the above 2 studies extraction was with DMSO rather than with PEG400.

Results: No visual signs of toxicity were reported in any of the test cultures. No reductions were observed in the mitotic indices of the cultures analyzed as compared with the solvent control cultures. Chromosomal aberrations analyzed from cultures treated with 25.0/2.5, 50.0/5.0, 75.0/7.5, and 100.0/10.0 ul/ml of saline/PEG or DMSO test material extracts demonstrated no significant increase in cells with chromosomal aberrations, polyploidy, or endoduplication as compared with solvent control cultures.

Summary: It was concluded that saline and DMSO extracts of DUROS implant components were negative for inducing chromosomal aberrations in CHO cells with and without metabolic activation.

Study title: Extracts of Tecophilic HP-60D-20 (Code No. 0003074, Control No. MV9720451): in vivo mouse micronucleus assay.

Study No.: TR-98-5904-011

Volume#/page #: 1.47/1

Conducting laboratory: _____

Date of study initiation/completion: 4-27-1998/11-10-1998

GLP compliance: Yes

QA report: Yes

Test article lot #: MV9720451

Study endpoint: micronucleated polychromatic erythrocytes

Methodology: Extracts of molded parts were evaluated for their in vivo clastogenic (chromosome breaking) activity and/or their ability to induce disruption of the mitotic apparatus by detecting micronuclei in polychromatic erythrocytes in the mouse bone marrow.

A single dose of the material extract or control article was administered by intravenous injection (saline) or intraperitoneal injection (sesame oil) to groups of CD-1 mice. Hind limb bones were extracted from euthanized mice either 24 or 48 hours later. The bone marrow from each mouse was flushed, centrifuged, smeared on slides, and stained. Eucleated immature RBC's [polychromatic erythrocytes (PCE)] were examined microscopically for the presence of micronuclei. Assay design was based on OECD Guidelines 474, 12/96 final draft. Extracts were prepared as described under Ames test.

Strain/species/cell lines: Crl:CD-1BR strain/mouse

Study design: was as follows:

Group #	Treatment	Acute treatment sampling time	
		24 hours	48 hours
1	Positive control	5	-
2	Vehicle control (saline)	5	5
3	Test article extract (saline)	5	5
4	Vehicle control (sesame oil)	5	5
5	Test article extract (sesame oil)	5	5

The dosing volume was 50 ml/kg. High dose was with undiluted extract.

Study acceptance criteria: vehicle control usually should be less than 0.4% micronucleated PCE's. Positive control response must be statistically significantly higher than the vehicle control group and be consistent with historical control data. High dose should be the neat (undiluted) extract. High dose should allow animal recovery and survival.

Criteria for positive clastogenic response: the detection of a statistically significant percentage of micronucleated PCE's above the sesame oil and saline control values for at least one dose level and a statistically significant dose-related response.

Results:

There were signs of clinical toxicity in animals treated with the saline or sesame oil control and saline and sesame oil extracts of the test articles.

As shown in table below, Tecophilic HP-60D-20 extracts were neither cytotoxic to the bone marrow (PCE:NCE ratio), nor they increased percentage of micronucleated PCE's.

Table 6. Effect of Tecophilic HP-60D-20 in mouse micronucleus assay

Treatment	Dose	Harvest time(h)	% micronucleated PCE's mean+SE of 2000/animal	Ratio PCE:NCE mean +SE	
Controls Vehicle Saline		24	0.04+0.02	0.25+0.05	
		48	0.05+0.02	0.31+0.04	
		Sesame oil	24	0.03+0.01	0.43+0.03
			48	0.02+0.01	0.26+0.04
Positive	80 mg/kg	24	3.46+0.33**	0.45+0.01	
Test article Extract Saline		24	0.01+0.01	0.33+0.03	
		48	0.05+0.02	0.39+0.04	
		Sesame oil	24	0.02+0.004	0.34+0.013
			48	0.05+0.00	0.36+0.04
Historical control data Vehicle controls			0.069+0.004	0.599+0.013	
		Positive CP controls	3.061+0.099**	0.615+0.024	

** Significantly different compared with vehicle controls. Positive control CP=cyclophosphamide

Findings for the other 2 implant components i.e. Petrothene LS6901-00 and C-Flex LS55A tested under studies #s TR-98-5904-008 and TR-98-5904-005 respectively were similar.

Summary: The saline and sesame oil extracts of all components of the DUROS implant were considered negative in the mouse bone marrow micronucleus test under the conditions of exposure in this assay.

Sponsor has also included results of the studies conducted in 1983 on Biocompatibility and safety evaluation of Tecoflex EG-60D and Tecoflex 80A. These studies were sponsored by Thermo Electron Corporation, Waltham, MA and were conducted by Bioassay Systems Corporation as projects numbers 11308 and 11945, respectively.

Both Tecoflex polyurethanes gave negative results in the following tests:

Systemic injection and intracutaneous tests:

In the systemic injection test in mice, test and control samples were injected i.v. when extracted in 0.9% saline and alcoholic sodium chloride and i.p. when extracted in PGE400 and cottonseed oil. The sample was extracted at a ratio of 6 cm²/ml of extractant at 50 °C for 72 hours. The dose was 50 ml/kg except for 10g/kg for PGE400. Mice were examined at 2, 24, 48 and 72 hours for physical signs of toxicity, aberrant behavior and deaths.

In the intracutaneous test in rabbits, 0.20 ml of the test sample was injected at 10 sites on one side and blanks on the contralateral side. Sites were examined at 24, 48 and 72 hours post-injection and scored for erythema and edema according to Draize scoring system. Sample was considered non toxic if difference between the test and control did not exceed 1.0.

Intramuscular implantation in rabbits: Solid strips of Tecoflex and USP negative reference plastic was implanted directly into the paravertebral muscle. Rabbits were sacrificed after 7 and 21 days for macroscopic and microscopic examination of the implant sites.

Agar overlay cytotoxicity test using L929: Test and control samples were placed directly on the agar surface. Each plate contained 2 test samples and a positive and a negative control. Plates were incubated for 24 hours and then examined microscopically for zones of decolorization and cell lysis. The degree of cytotoxicity was scored according to decolorization/lysis ratio. Only samples producing lysis scores of 1 or greater at any of test sites were considered cytotoxic.

Direct exposure cytotoxicity test: was conducted using confluent human diploid fibroblasts maintained in monolayer culture. Cell were incubated for 24 hours and then scored for cell lysis or vacuolization. Scores of 1 or greater were considered being cytotoxic.

Red blood cell hemolysis (direct contact): Freshly diluted, anticoagulated human blood was added to tubes containing 0.9% sodium chloride (negative control) or test sample in 0.9% sodium chloride or deionized water as positive control. After incubation for 60 minutes at 37 °C, tubes were centrifuged. The amount of hemoglobin released in the medium by RBCs was measured spectrophotometrically at 545 nm. A sample producing percentage hemolysis score of greater than 10% was considered toxic.

Ames/Salmonella mutagenicity test: Aliquots of saline extracted test sample (10, 30, 100, 300, or 1000 ul) or controls (100 or 1000 ul) were used. Samples were tested in duplicates in Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538, both in the presence and absence of rat liver metabolic activation system. A test sample was considered mutagenic if it induced a concentration-dependent response in which the number of revertants per plate exceeded 2 times the negative control mutation rate.

Results: Both Tecoflex EG-60D and Tecoflex 80A were negative in all of the above described tests.

Sponsor has also provided a list of FDA-approved medical devices currently using Tecoflex polyurethanes. These include catheters, surgical stents, fiber optic imaging, blood bags, canulas and naso-gastric tubes.

In addition the sponsor has provided an extensive nonclinical bibliography and references along with reprints of publications for the following components:

Titanium, polyurethane, high density polyethylene, thermoplastic elastomer (C-flex), silicon medical fluid, dimethyl sulfoxide, sodium chloride, magnesium stearate, polyvinylpyrrolidone (PVP), disodium carboxymethylcellulose and PEG-400.

Overall summary:

Leuprolide acetate, the drug substance being reviewed under this NDA is indicated for the treatment of advanced prostate cancer.

Leuprolide acetate is a synthetic nonapeptide of the naturally occurring gonadotropin-releasing hormone (Gn-RH of LH-RH). It is a Gn-RH agonist and possesses 80-100 times greater potency than the native GnRH.

Leuprolide acetate acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses resulting in suppression of ovarian and testicular steroidogenesis after an initial stimulation.

Leuprolide acetate is not active when given orally.

Daily injection and depot formulations of leuprolide acetate have been used in sex hormone ablation therapy since the introduction of this active substance to the market in the United States in 1985.

Leuprolide acetate as Lupron (TAP Holdings Inc) for injection and for depot suspension are FDA approved products under NDAs 19-010, 19-732, 19-943, 20-011, 20-263, 20-517 and 20-708 for many indications such as palliative treatment of prostate cancer, endometriosis, treatment of uterine fibroids, and precocious puberty.

At present leuprolide acetate as Lupron for the palliative treatment of prostate cancer is available either as one month or 4-month formulations and to maintain continuous therapeutic effectiveness these need to be administered every month or every 4 months, respectively.

DUROS Leuprolide Implant (Viadur), the formulation under consideration, is designed to be administered once a year.

Viadur is a nondegradeable, osmotically driven miniaturized implant designed to deliver leuprolide acetate continuously at a nominal rate of 120 ug/day over a period of one year.

The pharmacology, pharmacokinetics and toxicology of leuprolide acetate have been extensively studied in preclinical studies. Its safety and efficacy also have been well established in the clinical studies.

Viadur has been tested in long term studies in rats, dogs and swine for its local reaction. These studies demonstrated that the implant caused only mild to moderate local reaction and was deemed biocompatible. All components of Viadur were negative in a battery of genotoxicity tests.

Results of sponsor's conducted studies along with review of the submitted published literature provided good evidence for the safety of the proposed leuprolide formulation for the palliative treatment of advanced prostate cancer.

